Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1328	ubiquitin adj conjugating adj enzyme$1 or ubc$2	US-PGPUB; USPAT	OR	OFF	2005/05/02 10:02
L2	837636	gene$1 or sequence$1	US-PGPUB; USPAT	OR	OFF	2005/05/02 10:02
L3	184	1 near5 2	US-PGPUB; USPAT	OR	OFF	2005/05/02 10:03
L4	449	1 same human	US-PGPUB; USPAT	OR	OFF	2005/05/02 10:03
L5	104	3 and 4	US-PGPUB; USPAT	OR	OFF	2005/05/02 10:03

priority to 10/30/00

PGPUB-DOCUMENT-NUMBER: 20050079613

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20050079613 A1

TITLE: Downregulation of cell surface glycoproteins by a family of human ubiquitin ligases

PUBLICATION-DATE: April 14, 2005

INVENTOR-INFORMATION:

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APPL-NO: 10/ 624727

DATE FILED: July 21, 2003

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60397136 20020719 US

US-CL-CURRENT: 435/455, 435/226

ABSTRACT:

According to the present invention, eight human RING-CH-containing genes are human transmembrane ubiquitin ligase proteins, are homologues of the viral K3-family, and perform functions similar to their viral counterparts. One of these proteins, MARCH-IV, is able to downregulate MHC I and CD4 in a fashion similar to that afforded by the viral immune evasion proteins. This is the first cellular gene product identified that downregulates surface expression of MHC I. The MARCH-family of proteins regulates endocytosis of cell surface receptors (e.g., transferrin receptor, histocompatibility antigens and Fas; type I as well as type II transmembrane domains) via ubiquitination. Particular embodiments provide drug targets for inhibiting the internalization and degredation of various cell surface receptors. Further embodiments provide methods for treating or preventing cancer and other disorders (e.g., leukemia, mental retardation, and L-thalassemia), which methods comprise the administration of a MARCH antagonist or pharmaceutical composition thereof. Screening methods for identification of therapeutic compounds that are modifiers of MARCH activity, are also encompassed by the present invention.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of priority to U.S. Provisional Patent Application No. 60/397,136, filed 19 Jul. 2002.

---------- KWIC --------

Detail Description Paragraph - DETX (4):
[0064] MARCH-I and MARCH-II are mammalian members of the previously

described family of viral PHD/LAP domain proteins. Shared characteristics of this family are their amino-terminal PHD/LAP, or RING-CH domain, an even numbers of transmembrane segments, and the formation of high molecular weight complexes. In viruses, this family of ubiquitin ligases is thought to mediate the ubiquitination of the cytoplasmic tail of their target glycoproteins. Therefore, the cellular homologs are likely involved in the degradation of transmembrane proteins (such as MHC-I, ICAM-1 and B7.2). Further support for a role of this family in protein degradation comes from recent observations in yeast. Hochstrasser and colleagues observed that mutants in the Doa10/Ssm4 protein stabilized the shortlived transcription factor Mat2.alpha. as well as the ER-resident transmembrane ubiquitin conjugating enzyme ubc6 (Swanson, R. et al., Genes Dev. 15:2660-2674, 2001). Doa10 is related in sequence and predicted transmembrane topology to MARCH-VI, a human protein also called TEB-4 (Swanson, R. et al., 2001, supra). In contrast to the other MARCH-family members, MARCH-VI/TEB-4 encodes 12 predicted transmembrane domains. Whereas Doa10, and presumably MARCH-VI, locate to the ER, both MARCH-I and MARCH-II are localized to post-ER compartments. It could therefore be speculated that a Doa10-like molecule was the original precursor of this protein family, which then diversified for specific functions with respect to target proteins and subcellular location. Swanson et al. proposed the name RING-CH for the PHD/LAP-domain found in the Doa10 protein. Since RING-CH more accurately reflects the function of this domain as ubiquitin-ligase module and thus its functional relationship to the RING domain, it has been adopted herein.

Detail Description Paragraph - DETX (17):

[0077] The membrane association of MARCH-IV implies that the ubiquitin conjugating enzyme is membrane associated or needs to be recruited to the membrane. Indeed, experimental evidence suggests that SSM4/DOA10, p78 and Der3/Hrd1 cooperate with ubc6 and ubc7 (Bordallo et al., 1998, supra; Fang et al., 2001, supra; Gardner, R. G., G. M. Swarbrick, N. W. Bays, S. R. Cronin, S. Wilhovsky, L. Seelig, C. Kim and R. Y. Hampton, J. Cell. Biol. 151:69-82; 2000; Swanson et al., 2001, supra). Both E2s are bound to the ER-membrane via either a transmembrane domain or by interacting with another protein (Biederer, T., C. Volkwein and T. Sommer, Science 278:1806-1809, 1997; Sommer, T. and S. Jentsch, Nature 365:176-179, 1993). It is thus likely that MARCH-VI will interact with the human homologs of ubc6 or ubc7. MARCH-proteins that leave the ER and regulate internalization, however, can be assumed to interact with different E2s. These E2's would need to be accessible at the membrane compartments containing the MARCH-proteins.

Detail Description Paragraph - DETX (95):

[0155] N-terminal His.sub.6-tagged B2 constructs of human ubc6 and ubc7 were constructed using the NhcI and BamII sites of pET28 (Novagen, Inc. Madison, Wis.). The human ubc7 gene is a homologue of yeast Ubnc7 and is also called UBE2G2, to distinguish it from another human E2, namely UbCH7. cDNA for human ubc7 was obtained from the IMAGE consortium (clone ID 563616), through Research Genetics (Invitrogen, Carlsbad, Calif.). The following primers were purchased from Invitrogen: (hUbc6-forward: 5'-ATA TGC TAG CGC CAT GAG GAG CAC CAG CAG TAA G-3' (SEQ ID NO:63)), (hUbc6-REVERSE: 5'-ATA TGC ATC CTC ACT CCT GCG CGA TGC TCC TC-3' (SEQ ID NO:64)), (hUbc7-forward: 5'-ATA TGC TAG CGC CAT GGC GGG GAC CGC GCT CAA G-3' (SEQ ID NO:65)), (hUbc7-reverse:5'-ATA GGG ATC CTC ACA GTC CCA GAG ACT TCT GG-3' (SEQ ID NO:66)). DNA sequencing confirmed the sequence for human ubc-7. Sequencing of the human ubc6 clone showed that it differs from the sequence with the Accession number AF296658 by having three point insertions in the DNA region corresponding to amino acids 214 to 238. The resulting frameshifted sequence, with identical point insertions, is also found in a database entry NM-058167. All three variants of human ubc6 are identical in protein sequences between amino acids 45 and 213 (using the numbering from AF296658).

Detail Description Paragraph - DETX (132):

[0182] His.sub.6-tagged constructs of human ubc6 and ubc7 were expressed in BL21 DE3 cells, induced with 0.4 mM IPTG at OD.sub.600 of 0.6 for 3 hours. Cells were resuspended in PBS with 0.1% NP-40, incubated for 20 minutes on ice with lysozyme and then sonicated. The soluable fraction was loaded into Ni-NTA beads (Qiagen), washed with PBS and 20 mM Imidazole. Protein was buffer exchanged, and cluted with 50 mM Tris pH 7.5, 50 mM NaCl, 10% glycerol, 0.5 .beta.-mercapoethanol, and 200 mM Imidazole. Purified E3 proteins were stored at 4.degree. C. and E2 proteins were stored at -80.degree. C.

Detail Description Paragraph - DETX (141):

[0189] Representative results obtained with three human E2 enzymes UbCH2, UbCH3 and UbCH5a, are shown in FIG. 9. Anti-ubiquitin reactive high molecular weight complexes were not observed in the absence of E3-enzymes (FIG. 9), or in the presence of purified GST. The RiNG-CH-GST fusion proteins of all four MARCH-proteins tested were able to catalyze the formation of high-molecular weight molecular ubiquitin complexes in the presence of at least one of these three enzymes. The yield of these complexes, however, varied depending on the combination of MARCH-protein and E2 enzyme. MARCH-II was able to promote high molecular weight ubiquitinated complexes with several of the E2 enzymes tested. In comparison, MARCH-IV was mostly active with UbCH2. These results further demonstrate that MARCH proteins act as ubiquitin ligases. Moreover, the data show that the RING-CH domain acts as an ubiquitin ligase module.

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DOCUMENT-IDENTIFIER: US 20050064547 A1

TITLE: Vectors and transfected cells

PUBLICATION-DATE: March 24, 2005

INVENTOR-INFORMATION:

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APPL-NO: 10/ 668496

DATE FILED: September 24, 2003

US-CL-CURRENT: 435/69.1, 435/226 , 435/320.1 , 435/353 , 435/455 , 530/350 , 536/23.5

ABSTRACT:

Disclosed are vectors for cloning and expressing nucleic acid sequences, methods of transfecting cells with these vectors, transfected cells containing these vectors, and antibiotic resistance cassettes. For instance, the vector may include, from upstream to downstream, a first promoter, at least one cloning site, a rat Kv2.1 polyadenylation sequence, and an origin of replication. As another example, the vector includes, from upstream to downstream, a ubiquitin promoter, at least one cloning site, a first polyadenylation sequence, a first origin of replication, at least one SV40 promoter that includes an SV40 origin, a first antibiotic resistance marker, a second polyadenylation sequence, a third polyadenylation sequence, a second origin of replication, and a second antibiotic resistance marker.

---------- KWIC ---------

Detail Description Paragraph - DETX (20):

[0048] The promoter may be a ubiquitin promoter, such as a human ubiquitin promoter, such as a human ubiquitin C (UbC) promoter. The human UbC promoter permits overexpression of recombinant protein in a broad range of mammalian cell types. HERSKO et al., Ann. Rev. Biochem., 51:335-364 (1982); WULFF et al., FEBS Lett., 261:101-105 (1990); and SCHORPP et al., Nuc. Acids Res., 24:1787-1788 (1996).

Detail Description Paragraph - DETX (50):

[0078] Still another example of a vector with at least one cloning site, but without a gene of interest, is one having, from upstream to downstream, a UbC promoter, multiple cloning sites, a Kv2.1 polyadenylation sequence, an f1 origin, a first SV40 promoter that includes a first SV40 origin, a neomycin resistance gene, a TK polyadenylation sequence, an SV40 polyadenylation sequence, a pMB1 origin, and an ampicillin resistance gene.

PGPUB-DOCUMENT-NUMBER: 20050059803

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20050059803 A1

TITLE: Immunosuppressant target proteins

PUBLICATION-DATE: March 17, 2005

INVENTOR-INFORMATION:

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APPL-NO: 10/ 877320

DATE FILED: June 24, 2004

RELATED-US-APPL-DATA:

child 10877320 A1 20040624

parent continuation-of 09517491 20000302 US PENDING

child 09517491 20000302 US

parent continuation-of 08360144 19941220 US GRANTED

parent-patent 6150137 US

child 08360144 19941220 US

parent continuation-in-part-of 08250795 19940527 US PENDING

US-CL-CURRENT: 530/350

ABSTRACT:

The present invention relates to the discovery of novel proteins of mammalian origin which are immediate downstream targets for FKBP/rapamycin complexes.

RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. Ser. No. 08/250,795, filed May 27, 1994 and entitled "Immunosuppressant Target Proteins", the specification of which are incorporated by reference herein.

---------- KWIC --------

Summary of Invention Paragraph - BSTX (11):

[0010] The present invention relates to the discovery of novel proteins of mammalian origin which are immediate downstream targets for FKBP/rapamycin complexes. As described herein, a drug-dependent interaction trap assay was used to isolate a number of proteins which interact with an FK506-binding

protein/rapamycin complex, and which are collectively referred to herein as "RAP-binding proteins" or "RAP-BPs". In particular, mouse and human genes have been cloned for a protein (referred to herein as "RAPT1") which is apparently related to the yeast TOR1 and TOR2 gene products. Furthermore, a novel ubiquitin-conjugating enzyme (referred to herein as "rap-UBC") has been cloned based on its ability to bind FKBP/rapamycin complexes. In addition, a RAPT1-like protein was cloned from the human pathogen Candida albicans. The present invention, therefore, makes available novel proteins (both recombinant and purified forms), recombinant genes, antibodies to RAP-binding proteins, and other novel reagents and assays for diagnostic and therapeutic use.

Summary of Invention Paragraph - BSTX (20):

[0019] In yet other preferred embodiments, the rap-UBC protein is a recombinant fusion protein which includes a second polypeptide portion, e.g., a second polypeptide having an amino acid sequence unrelated to the rap-UBC sequence, e.g. the second polypeptide portion is glutathione-S-transferase, e.g. the second polypeptide portion is a DNA binding domain of transcriptional regulatory protein, e.g. the second polypeptide portion is an RNA polymerase activating domain, e.g. the fusion protein is functional in a two-hybrid assay.

Summary of Invention Paragraph - BSTX (30):

[0029] Another aspect of the present invention provides a substantially isolated nucleic acid having a nucleotide sequence which encodes a rap-UBC polypeptide. In preferred embodiments: the encoded polypeptide specifically binds a rapamycin complexes and/or is able to either agnoize or antagonize assembly of rapamycin-containing protein complexes. The coding sequence of the nucleic acid can comprise a rap-UBC-encoding sequence which can be identical to the cDNA shown in SEQ ID No: 23, or it can merely be homologous to that sequence. For instance, the rap-UBC-encoding sequence preferably has a sequence at least 60% homologous to the nucleotide sequences in SEQ ID No: 23, though higher sequence homologies of, for example, 80%, 90% or 95% are also contemplated. The nucleic acid can comprise the nucleotide sequence represented in SEQ ID No: 23, or it can comprise a fragment of that nucleic acid, which fragment may be, for instance, encode a fragment of which is, for example, at least 5, 10, 20, 50, or 100 amino acids in length. The polypeptide encoded by the nucleic -acid can be either an agonist [e.g. mimics), or alternatively, an antagonist of a biological activity of a naturally occuring form of the rap-UBC protein, e.g., the polypeptide is able to modulate rapamycin-mediated protein complexes.

Summary of Invention Paragraph - BSTX (31):

[0030] Furthermore, in certain preferred embodiments, the subject rap-UBC nucleic acid will include a transcriptional regulatory sequence, e.g. at least one of a transcriptional promoter or transcriptional enhancer sequence, which regulatory sequence is operably linked to the rap-UBC gene sequence. Such regulatory sequences can be used in to render the rap-UBC gene sequence suitable for use as an expression vector.

Detail Description Paragraph - DETX (6):

[0051] As described herein, the present invention relates to the discovery of novel proteins of mammalian origin which are immediate downstream targets for FKBP/rapamycin complexes. As described below, a drug-dependent interaction trap assay was used to isolate a number of proteins which bind the FKBP12/rapamycin complex, and which are collectively referred to herein as "RAP-binding proteins" or "RAP-BPs". In particular, mouse and human genes have been cloned for a protein (referred to herein as "RAPT1") which is apparently related to the yeast TOR1 and TOR2 gene products. Furthermore, a novel ubiquitin-conjugating enzyme (referred to herein as "rap-UBC") has been cloned based on its ability to bind FKBP/rapamycin complexes. The present invention,

therefore, makes available novel proteins (both recombinant and purified forms), recombinant genes, antibodies to RAP-binding proteins, and other novel reagents and assays for diagnostic and therapeutic use. Moreover, drug discovery assays are provided for identifying agents which can modulate the binding of one or more of the subject RAP-binding proteins with FK506-binding proteins. Such agents can be useful therapeutically to alter the growth and/or differentiation of a cell, but can also be used in vitro as cell-culture additives for controlling proliferation and/or differentiation of cultured cells and tissue. Other aspects of the invention are described below or will be apparent to those skilled in the art in light of the present disclosure.

Detail Description Paragraph - DETX (25):

[0070] As described below, one aspect of this invention pertains to an isolated nucleic acid comprising the nucleotide sequence encoding a RAP-binding protein, fragments thereof, and/or equivalents of such nucleic acids. The term nucleic acid as used herein is intended to include such fragments and equivalents. The term equivalent is understood to include nucleotide sequences encoding functionally equivalent RAP-binding proteins or functionally equivalent peptides which, for example, retain the ability to bind to the FKBP/rapamycin complex, and which may additionally retain other activities of a RAP-binding protein such as described herein. Equivalent nucleotide sequences will include sequences that differ by one or more nucleotide substitutions, additions or deletions, such as allelic variants; and will also include sequences that differ from the nucleotide sequence of the mammalian RAPT1 genes represented in SEQ ID No: 1 or SEQ ID No. 11, or the nucleotide sequence of the fungal RAPT1 protein of SEQ ID No. 13, or the nucleotide sequence encoding the UBC enzyme represented in SEQ ID No. 23, due to the degeneracy of the genetic code. Equivalent nucleic acids will also include nucleotide sequences that hybridize under stringent conditions (i.e., equivalent to about 20-27.degree. C. below the melting temperature (T.sub.m) of the DNA duplex formed in about 1 M salt) to a nucleotide sequence of a RAPT1 protein comprising either the sequence shown in SEQ ID No: 2 or 12, or to a nucleotide sequence of the RAPT1 gene insert of pIC524 (ATCC accession no. 75787). Likewise, equivalent nucleic acids encoding homologs of the subject rap-UBC enzyme include nucleotide sequences that hybridize under stringent conditions to a nucleotide sequence represented in SEQ ID No. 23, or to a nucleotide sequence of the rap-UBC gene insert of SMR4-15 (ATCC accession no. 75786). In one embodiment, equivalents will further include nucleic acid sequences derived from, and evolutionarily related to, a nucleotide sequence comprising that shown in either SEQ ID No. 1, or SEQ ID No. 11, or SEQ ID No. 13, or SEQ ID No.23.

Detail Description Paragraph - DETX (27):

[0072] Likewise, the amino acid sequence shown in SEQ ID No. 24 represents a biologically active portion of a larger full-length form of a human ubiquitin-conjugating enzyme. Accordingly, preferred embodiments of the subject rap-UBC comprise at least a portion of the amino acid sequence of SEQ ID No. 24 (or of the rap-UBC gene insert of SMR4-15 described in Example 5) which possess either the ability to bind a FKBP/rapamycin complex or the ability to conjugating ubiquitin to a cellular protein, or both. Given that rapamycin causes a block in the cell-cycle during G1 phase, it is probable that the spectrum of biological activity of the subject rap-UBC enzyme includes control of half-lives of certain cell cycle regulatory proteins, particularly relatively short lived proteins (e.g. proteins which have half-lives on the order of 30 minutes to 2 hours). For example, the subject UBC may have the ability to mediate ubiquitination of, for example, p53, myc and/or cyclins, and therefore affects the cellular half-life of a cell-cycle regulatory protein in proliferating cells. The binding of the rap-UBC to the FKBP/rapamycin complex may result in sequestering of the enzyme away from its substrate proteins. Thus, rapamycin may intefere with the ubiquitin-mediated degradation of p53 in

a manner which causes cellular p53 levels to rise which in turn inhibits progression of the G1 phase.

Detail Description Paragraph - DETX (31):
[0076] The nucleotide sequence shown in SEQ ID No: 23 encodes a biologically active portion of the human rap-UBC enzyme. Accordingly, in one embodiment of the present invention, the nucleic acid is a cDNA encoding a peptide including an amino acid sequence substantially homologous to that portion of the rap-UBC protein represented by SEQ ID No: 24. Preferably, the nucleic acid is a cDNA molecule comprising at least a portion of the nucleotide sequence shown in SEQ ID No: 23. Preferred nucleic acids encode a peptide comprising an amino acid sequence which is at least 60% homologous, more preferably 70% homologous and most preferably 80% homologous with an amino acid sequence shown in SEQ ID No: 24. Nucleic acids encoding polypeptides, particularly those having a ubiquitin conjugating activity, and comprising an amino acid sequence which is at least about 90%, more preferably at least about 95%, and most preferably at least about 98-99% homologous with a sequence shown in SEQ ID No: 24 are also within the scope of the invention.

Detail Description Paragraph - DETX (58):
[0103] Likewise, preferred embodiments of recombinant rap-UBC proteins include an amino acid sequence which is at least 70% homologous, more preferably 80% homologous, and most preferably 90% homologous with an amino acid sequence represented by SEQ ID No. 24. Recombinant rap-UBC proteins which are identical, or substantially identical (e.g. 95 to 98% homologous) with an amino acid sequence of SEQ ID No. 24 are also specifically contemplated by the present invention.

Detail Description Paragraph - DETX (115):
[0160] Furthermore, inhibitors of the enzymatic activity of each of the subject RAP-binding proteins can be identified using assays derived from measuring the ability of an agent to inhibit catalytic conversion of a substrate by the subject proteins. For example, the ability of the subject RAPT1 proteins to phosphorylate a phosphatidylinositol substrate, such as phosphatidylinositol-4,5-biphosphate (PIP2), in the presence and absence of a candidate inhibitor, can be determined using standard enzymatic assays. Likewise, the ability of the subject ubiquitin-conjugating enzyme to accept ubiquitin (e.g. from an E1:Ub conjugate) or subsequently transfer ubiquitin to a substrate protein, can be readily ascertained in the presence and absence of a candidate inhibitor. Exemplary assays in which the rapUBC enzyme of the present invention can be used are set forth in U.S. patent application Ser. No. 08/176,937, entitled "Assay and Reagents for Detecting Inhibitors of Ubiquitin-dependent Degradation of Cell Cycle Regulatory Proteins", the specification of which was filed Jan. 4, 1994, and U.S. patent application Ser. No. 08/247,904, entitled "Human Ubiquitin Conjugating Enzyme" the specification of which was filed May 23, 1994.

Detail Description Paragraph - DETX (177):
Cloning of Novel Human Ubiquitin Conjugating Enzyme

Detail Description Paragraph - DETX (178):
[0212] Constructs similar to those described above for the drug-dependent interaction trap assay were used to screen a W138 (mixed G.sub.0 and dividing fibroblast) cDNA library (Clonetech, Palo Alto Calif.) in pGADGH (XhoI insert, Clonetech). Briefly, the two hybrid assay was carried out as above, using GAL4 constructs instead of LexA, and in an HF7C yeast cell (Clonetech) in which FKB1 gene was disrupted (see Example 1). Of the clones isolated, a novel human ubiquitin-conjugating enzyme (rap-UBC) has been identified. A deposit of the pGADGH plasmid (clone "SMR4-I5") was made with the American Type Culture

Collection (Rovkville, Md.) on May 27, 1994, under the terms of the Budapest Treaty. ATCC Accession number 75786 has been assigned to the deposit. The insert is approximately 1 kB.

Detail Description Paragraph - DETX (179):

[0213] The sequence of the 5' portion of the SMR4-15 insert is given by SEQ ID No. 23 (nucleotide) and SEQ ID No. 24 (amino acid) and comprises a substantial portion of the coding region for rap-UBC, including the active site cysteine. The sequence for the 3' portion of the clone is provided by SEQ ID No. 25. As described above, primers based on the nucleic acid sequence of SEQ ID No. 23 (and 25) can be used to amplify fragments of the rap-UBC gene from SMR4-15. The PCR primers can be subsequently sub-cloned into expression vectors, and used to produce recombinant forms of the subject enzyme. Thus, the present provides recombinant rap-UBC proteins encoded by recombinant genes comprising rap-UBC nucleotide sequences from ATCC deposit number 75786.

PGPUB-DOCUMENT-NUMBER: 20050014206

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20050014206 A1

TITLE: Method of identifying compounds that specifically inhibit the anaphase promoting complex

PUBLICATION-DATE: January 20, 2005

INVENTOR-INFORMATION:

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APPL-NO: 10/ 825688

DATE FILED: April 16, 2004

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60472728 20030523 US

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	DOC-ID	APPL-DATE
DE	EP 03 008 908.0	2003DE-EP 03 008 908.0	April 16, 2003

US-CL-CURRENT: 435/7.21, 514/2

ABSTRACT:

A screening method for identifying specific APC inhibitors comprises a primary screen in which a compound is tested for its ability to interfere with binding of CDH1 or CDC20 to the APC and a secondary screen, in which the compound is tested for its ability to interfere with the activation of the APC by CDH1 or CDC20.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the priority benefit of U.S. Provisional Application No. 60/472,728, filed May 23, 2003, herein incorporated by reference in its entirety.

---------- KWIC ---------

Detail Description Paragraph - DETX (47):

[0081] An example for an ubiquitin conjugating enzyme (E2) is, in a preferred embodiment, the human variant UBCH5b (gene bank accession number U39317), although, also in this case, UBCH5b homologs from other species, e.g. Xenopus laevis, may be employed. Alternatively, UBCH5a or UBCH5c can be used. Preferably the ubiquitin conjugating enzyme E2 is fused to an affinity tag.

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PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040219516 A1

TITLE: Viral vectors containing recombination sites

PUBLICATION-DATE: November 4, 2004

INVENTOR-INFORMATION:

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APPL-NO: 10/ 622088

DATE FILED: July 18, 2003

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60474940 20030603 US

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non-provisional-of-provisional 60456496 20030324 US

non-provisional-of-provisional 60398617 20020726 US

non-provisional-of-provisional 60396335 20020718 US

US-CL-CURRENT: 435/5, 435/320.1 , 435/325 , 435/456 , 435/69.3 , 530/350 , 536/23.72

ABSTRACT:

The present invention provides compositions and methods for the construction of nucleic acids comprising all or portion of a viral genome. Nucleic acid molecules of the invention may be constructed to contain multiple recombination and/or topoisomerase recognition sites. The compositions include vectors having multiple recombination sites with unique specificity that contain all or a portion of a viral genome. The methods permit the insertion of a sequence of interest into a viral genome using recombinational and/or topoisomerase-mediated cloning. The present invention also provides methods of constructing recombinant virus, methods of expressing polypeptides, and methods of expressing fusion polypeptides.

---------- KWIC ---------

Brief Description of Drawings Paragraph - DRTX (56):

[0122] FIG. 46B shows the recombination region of the expression clone resulting from pLenti6/UbC/V5-DEST.times.entry clone. FIG. 46C shows the

complete sequence of the UbC promoter.

Detail Description Paragraph - DETX (580):
[0702] A four plasmid co-transfection is used to create infectious lentiviral vectors (Dull, et al., (1998) J. Virol. 72:8463-8471). One of the vectors (pLenti6/V5-DEST, pLenti6/V5-D-TOPO.RTM., pLenti4/V5-DEST, or pLenti6/UbC/V5-DEST) contains the gene of interest and is packaged into the virions (for vector maps, see FIGS. 36A-D). The other three plasmids are co-transfected to supply the viral proteins in trans. None of these three vectors are packaged into the virions. Each vector and a description of its features is described in more detail below. Vector maps are provided as FIGS. 37A, 37B, and 37C.

Detail Description Paragraph - DETX (730):
[0848] The pLenti6/V5-DEST , pLenti4/V5-DEST, and pLenti6/UbC/V5-DEST vectors are designed for use with the ViraPower.TM. Lentiviral Expression System available from Invitrogen Corporation, Carlsbad, Calif., which is discussed in some detail above. Depending on the vector chosen, the pLenti-DEST vectors are available with the human cytomegalovirus (CMV) immediate early promoter or the human ubiquitin C (UbC) promoter to control expression of the gene of interest, and the Zeocin.TM. resistance gene or the blasticidin resistance gene for selection in E. coli or mammalian cells.

Detail Description Paragraph - DETX (733):
[0851] The pLenti-DEST vectors contain the following features: Rous Sarcoma Virus (RSV) enhancer/promoter for Tat-independent production of viral mRNA in the producer cell line (Dull et al., 1998); modified HIV-1 5' and 3' Long Terminal Repeats (LTR) for viral packaging and reverse transcription of the viral mRNA (Dull et al., 1998; Luciw, 1996) (Note: The U3 region of the 3' LTR is deleted (.DELTA.U3) and facilitates self-inactivation of the 5' LTR after transduction to enhance the biosafety of the vector (Dull et al., 1998)); HIV-1 psi (.PSI.) packaging sequence for viral packaging (Luciw, 1996); HIV Rev response element (RRE) for Rev-dependent nuclear export of unspliced viral mRNA (Kjems et al., 1991, Proc. Natl. Acad. Sci. USA 88, 683-687; Malim et al., 1989, Nature 338, 254-257); human CMV or UbC promoter for constitutive expression of the gene of interest from a viral or cellular promoter, respectively; two recombination sites, attR1 and attR2, downstream of the CMV or UbC promoter for recombinational cloning of the gene of interest from an entry clone; chloramphenicol resistance gene (Cm.sup.R) located between the two attR sites for counterselection; the ccdB gene located between the attR sites for negative selection; C-terminal V5 epitope for detection of the recombinant protein of interest (Southern et al., 1991, J. Gen. Virol. 72, 1551-1557); blasticidin (Izumi et al., 1991; Kimura et al., 1994; Takeuchi et al., 1958; Yamaguchi et al., 1965) or Zeocin.TM. (Drocourt et al., 1990, Nucleic Acids Res. 18, 4009; Mulsant et al., 1988, Somat. Cell Mol. Genet. 14, 243-252) resistance gene for selection in E. coli and mammalian cells; ampicillin resistance gene for selection in E. coli; and the pUC origin for high-copy replication of the plasmid in E. coli.

Detail Description Paragraph - DETX (736):
[0854] The pLenti6/UbC/V5-DEST vector uses the human UbC promoter to allow constitutive, but more physiological levels of expression from the gene of interest in mammalian cells (Marinovic et al., 2000, Biophys. Res. Comm. 274, 537-541). The sequence of the pLenti6/UbC/V5-DEST plasmid is provided as Table 20. When compared to the CMV promoter, the UbC promoter is generally 2-4 fold less active. The UbC promoter is not down-regulated, making it useful for transgenic studies (Gill et al., 2001, Gene Ther. 8, 1539-1546; Lois et al., 2002, Science 295, 868-872; Marinovic et al., 2000; Schorpp et al., 1996, Nuc. Acids Res. 24, 1787-1788; Yew et al., 2001, Mol. Ther. 4, 75-82). The human

ubiquitin C (UbC) promoter (in pLenti6/UbC/V5-DEST) allows high-level expression of recombinant protein is most mammalian cell lines (Wulffet al., 1990, FEBS Lett. 261, 101-105) and in virtually all tissues tested in transgenic mice (Schorpp et al., 1996). The diagram below shows the features of the UbC promoter as described by Nenoi et al., 1996 Gene 175, 179-185.

Detail Description Paragraph - DETX (748):

[0866] FIG. 46B shows the recombination region of the expression clone resulting from pLenti6/UbC/V5-DEST.times. entry clone. Note that this diagram does not contain the complete sequence of the UbC promoter. For a diagram of the UbC promoter see FIG. 46C. Shaded regions in FIG. 46B correspond to those DNA sequences transferred from the entry clone into the pLenti6/UbC/V5-DEST vector by recombination. Non-shaded regions are derived from the pLenti6/UbC/V5-DEST vector. Bases 3079 and 4762 of the pLenti6/UbC/V5-DEST sequence are marked.

Detail Description Paragraph - DETX (750):

[0868] To confirm that a gene of interest is in frame with the C-terminal tag, sequence the expression construct, if desired. Refer to FIG. 46 for the location of the recommended primer binding sites (CMV or UbC forward priming site and V5(C-term) reverse priming site) to use to sequence the expression construct. To sequence a pLenti4/V5-DEST or pLenti6/V5-DEST construct, the CMV forward primer 5'-CGCAAATGGGCGGTAGGCGTG-3' and V5(C-term) reverse primer 5'-ACCGAGGAGAGGGTTAGGGAT-3' can be used. To sequence a pLenti6/UbC/V5-DEST construct, the UB forward primer 5'-TCAGTGTTAGACTAGTAAATTG-3' and the V5(C-term) reverse primer 5'-ACCGAGGAGAGGGTTAGGGAT-3' can be used.

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INVENTOR-INFORMATION:

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ABSTRACT:

Methods and reagents for the detection and selection of two interacting-polypeptides, especially integral membrane proteins and transcription factors, by monitoring the reassembly of ubiquitin amino-terminal and carboxy-terminal chimeric polypeptide fragments are disclosed. Negative selection against an N-end rule-labilized marker released following ubiquitin reassembly allows direct selection of the interacting polypeptide pair. Methods to identify agonists and antagonists for certain protein-protein interactions; methods and reagents/kits for identifying proteins that binds a target protein are also provided. The dynamic and adaptable nature of the assay allows adaptation to a number of applications--such as probing the molecular environment of cellular membrane proteins in vivo.

REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to Provisional application 60/223,41 1, filed on Aug. 4, 2000, the specification of which is incorporated by reference herein.

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Detail Description Paragraph - DETX (58):

[0129] The ubiquitins are a class of proteins found in all eukaryotic cells. The ubiquitin polypeptide is characterized by a carboxy-terminal glycine residue that is activated by ATP to a high-energy thiol-ester intermediate in a reaction catalyzed by a ubiquitin-activating enzyme (E1). The activated ubiquitin is transferred to a substrate polypeptide via an isopeptide bond between the activated carboxy-terminus of ubiquitin and the epsilon-amino group

of a lysine residue(s) in the protein substrate. This transfer requires the action of ubiquitin conjugating enzymes such as E2 and, in some instances, E3 activities. The ubiquitin modified substrate is thereby altered in biological function, and, in some instances, becomes a substrate for components of the ubiquitin-dependent proteolytic machinery which includes both UBP enzymes as well as proteolytic proteins which are subunits of the proteasome. As used herein, the term "ubiquitin" includes within its scope all known as well as unidentified eukaryotic ubiquitin homologs of vertebrate or invertebrate origin which can be classified as equivalents of human ubiquitin. Examples of ubiquitin polypeptides as referred to herein include the human ubiquitin polypeptide which is encoded by the human ubiquitin encoding nucleic acid sequence (GenBank Accession Numbers: U49869, X04803). Equivalent ubiquitin polypeptide encoding nucleotide sequences are understood to include those sequences that differ by one or more nucleotide substitutions, additions or deletions, such as allelic variants; as well as sequences which differ from the nucleotide sequence encoding the human ubiquitin coding sequence due to the degeneracy of the genetic code. Another example of a ubiquitin polypeptide as referred to herein is murine ubiquitin which is encoded by the murine ubiquitin encoding nucleic acid sequence (GenBank Accession Number: X51730). It will be readily apparent to the person skilled in the art how to modify the methods and reagents provided by the present inevntion to the use of ubiquitin polypeptides other than human ubiquitin.

Detail Description Paragraph - DETX (62):

[0133] The term "ubiquitin conjugation machinery" as used herein refers to a group of proteins which function in the ATP-dependent activation and transfer of ubiquitin to substrate proteins. The term thus encompasses: E1 enzymes, which transform the carboxy-terminal glycine of ubiquitin into a high energy thiol intermediate by an ATP-dependent reaction; E2 enzymes (the UBC genes), which transform the E1-S.about.Ubiquitin activated conjugate into an E2-S.about.Ubiquitin intermediate which acts as a ubiquitin donor to a substrate, another ubiquitin moiety (in a poly-ubiquitination reaction), or an E3; and the E3 enzymes (or ubiquitin ligases) which facilitate the transfer of an activated ubiquitin molecule from an E2 to a substrate molecule or to another ubiquitin moiety as part of a polyubiquitin chain. The term "ubiquitin conjugation machinery", as used herein, is further meant to include all known members of these groups as well as those members which have yet to be discovered or characterized but which are sufficiently related by homology to known ubiquitin conjugation enzymes so as to allow an individual skilled in the art to readily identify it as a member of this group. The term as used herein is meant to include novel ubiquitin activating enzymes which have yet to be discovered as well as those which function in the activation and conjugation of ubiquitin-like or ubiquitin-related polypeptides to their substrates and to poly-ubiquitin-like or poly-ubiquitin-related protein chains.

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TITLE: Methods for the identification, assessment, and treatment of patients with proteasome inhibition therapy

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INVENTOR-INFORMATION:

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DATE FILED: December 4, 2003

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US-CL-CURRENT: 424/155.1, 435/6

ABSTRACT:

The present invention is directed to the identification of markers that can be used to determine whether patients with cancer are clinically responsive or non-responsive to a therapeutic regimen prior to treatment. In particular, the present invention is directed to the use of certain combinations of markers, wherein the expression of the markers correlates with responsiveness or non-responsiveness to a therapeutic regimen comprising proteasome inhibition. Thus, by examining the expression levels of individual markers and those comprising a marker set, it is possible to determine whether a therapeutic agent, or combination of agents, will be most likely to reduce the growth rate of tumors in a clinical setting.

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/431,514, filed Dec. 6, 2002, the contents of which are incorporated herein by this reference.

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Detail Description Table CWU - DETL (17):
sapiens] 564 203574_at NM_005384.1 nuclear factor, interleukin 3 regulated NFIL3 >1 565 222146_s_at AK026674.1 transcription factor 4 TCF4 <1 566 227665_at BE968576 Homo sapiens, clone IMAGE: 4152387, mRNA -- <1 567 207995_s_at NM_014257.1 CD209 antigen-like CD209L <1 568 201097_s_at NM_001660.2 ADP-ribosylation factor 4 ARF4 <1 569 203975_s_at BF000239 chromatin assembly factor 1, subunit A (p150) CHAF1A >1 570

209136_s_at BG390445 ubiquitin specific protease 10 USP10 >1 571 238086_at AI288372 EST -- >1 572 242388_x_at AW576600 EST -- <1 573 241876_at AW663060 EST -- <1 574 228195_at BE645119 EST -- <1 575 202334_s_at AA877765 ubiquitin-conjugating enzyme E2B (RAD6 homolog) UBE2B <1 576 201472_at NM_003372.2 von Hippel-Lindau binding protein 1 VBP1 <1 577 217092_x_at AL031589 -- -- >1 578 208744_x_at BG403660 heat shock 105 kDa/110 kDa protein 1 HSPH1 >1 579 212412_at AV715767 Homo sapiens mRNA; cDNA DKFZp564A072 (from clone -- <1 DKFZp564A072) 580 217995_at NM_021199.1 sulfide quinone reductase-like (yeast) SQRDL <1 581 203275_at NM_002199.2 interferon regulatory factor 2 IRF2 <1 582 207335_x_at NM_007100.1 ATP synthase, H+ transporting, mitochondrial F0 complex, subunit e ATP5I >1 583 218130_at NM_024510.1 hypothetical protein MGC4368 MGC4368 >1 584 208914_at NM_015044.1 golgi associated, gamma adaptin ear containing, ARF binding protein 2 GGA2 <1 585 202985_s_at NM_004873.1 BCL2-associated athanogene 5 BAG5 >1 586 206587_at NM_006584.1 chaperonin containing TCP1, subunit 6B (zeta 2) CCT6B <1 587 223419_at BC004290.1 hypothetical protein MGC10870 MGC10870 >1 588 213102_at Z78330 ARP3 actin-related protein 3 homolog (yeast) ACTR3 <1 589 226520_at AI831506 EST -- <1 590 201366_at NM_004034.1 annexin A7 ANXA7 <1 591 213021_at AI741876 Homo sapiens mRNA; cDNA DKFZp566B213 (from clone DKFZp566B213) -- <1 592 201172_x_at NM_003945.1 ATPase, H+ transporting, lysosomal 9 kDa, V0 subunit e ATP6V0E <1 593 213295_at AA555096 Homo sapiens mRNA; cDNA DKFZp586D1122 (from clone -- <1 DKFZp586D1122) 594 226406_at AI823360 hypothetical protein MGC12909 MGC12909 <1 595 210564_x_at AF009619.1 CASP8 and FADD-like apoptosis regulator CFLAR <1 596 242606_at AL043482 EST -- <1 597 203292_s_at NM_021729.2 vacuolar protein sorting 11 (yeast) VPS11 >1 598 202579_x_at NM_006353.1 high mobility group nucleosomal binding domain 4 HMGN4 <1 599 229113_s_at W16779 protein kinase C, zeta PRKCZ >1 600 244743_x_at AA114243 zinc finger protein 138 (clone pHZ-32) ZNF138 <1 601 222622_at BG284709 hypothetical protein LOC283871 LOC283871 >1 602 210312_s_at BC002640.1 hypothetical protein LOC90410 LOC90410 <1 603 221530_s_at AB044088.1 basic helix-loop-helix domain containing, class B, 3 BHLHB3 <1 604 201994_at NM_012286.1 mortality factor 4 like 2 MORF4L2 <1 605 227262_at BE348293 Homo sapiens proteoglycan link protein mRNA, complete cds. -- >1 606 203693_s_at NM_001949.2 E2F transcription factor 3 E2F3 <1 607 221750_at BG035985 3-hydroxy-3-methylglutaryl-Coe- nzyme A synthase 1 (soluble) HMGCS1 <1 608 214789_x_at AA524274 Splicing factor, arginine/serine-rich, 46 kD SRP46 <1 609 200761_s_at NM_006407.2 vitamin A responsive; cytoskeleton related JWA <1 610 212233_at AL523076 Homo sapiens cDNA FLJ30550 fis, clone BRAWH2001502. -- <1 611 209300_s_at BC002888.1 DKFZP566B183 protein DKFZP566B183 <1 612 213708_s_at N40555 transcription factor-like 4 TCFL4 <1 613 207467_x_at NM_001750.2 calpastatin CAST <1 614 225414_at AL558987 hypothetical protein LOC284996 LOC284996 <1 615 235104_at BG292389 EST -- <1 616 214003_x_at BF184532 ribosomal protein S20 RPS20 >1 617 201542_at AY008268.1 SAR1 protein SAR1 <1 618 211316_x_at AF009616.1 CASP8 and FADD-like apoptosis regulator CFLAR <1 619 221522_at AL136784.1 hypothetical protein DKFZp434L0718 DKFZP434L0718 <1 620 210844_x_at D14705.1 catenin (cadherin-associated protein), alpha 1, 102 kDa CTNNA1 <1 621 210448_s_at U49396.1 purinergic receptor P2X, ligand-gated ion channel, 5 P2RX5 <1 622 212843_at AA126505 neural cell adhesion molecule 1 NCAM1 <1 623 224284_x_at AF338193.1 -- -- >1 624 222650_s_at BE898559 SLC2A4 regulator SLC2A4RG >1 625 212719_at AB011178.1 pleckstrin homology domain containing, family E (with leucine rich repeats) PLEKHE1 >1 member 1 626 38069_at Z67743 chloride channel 7 CLCN7 >1 627 233625_x_at AK021939.1 hypothetical protein FLJ20542 FLJ20542 >1 628 205053_at NM_000946.1 primase, polypeptide 1, 49 kDa PRIM1 >1 629 239749_at AW205090 EST -- >1 630 34764_at D21851 leucyl-tRNA synthetase, mitochondrial LARS2 >1 631 205659_at NM_014707.1 histone deacetylase 9 HDAC9 <1 632 242092_at AA019300 EST, Moderately similar to hypothetical

protein FLJ20097 [Homo sapiens] -- >1 [H. sapiens] 633 203575_at NM_001896.1 casein kinase 2, alpha prime polypeptide CSNK2A2 >1 634 221297_at NM_018654.1 G protein-coupled receptor, family C, group 5, member D GPRC5D <1 635 212900_at BE645231 SEC24 related gene family, member A (S. cerevisiae) SEC24A <1 636 230036_at BE669858 hypothetical protein FLJ39885 FLJ39885 <1 637 213101_s_at Z78330 ARP3 actin-related protein 3 homolog (yeast) ACTR3 <1 638 222846_at AB038995.1 RAB-8b protein LOC51762 <1 639 213455_at W87466 pleckstrin homology domain containing, family B (evectins) member 2 PLEKHB2 <1 640 242613_at AI809536 EST -- >1 641 218206_x_at NM_016558.1 SCAN domain containing 1 SCAND1 >1 642 222014_x_at AI249752 MTO1 protein MTO1 <1 643 212219_at D38521.1 proteasome activator 200 kDa PA200 <1 644 219806_s_at NM_020179.1 FN5 protein FN5 <1 645 218875_s_at NM_012177.1 F-box only protein 5 FBXO5 >1 646 208485_x_at NM_003879.1 CASP8 and FADD-like apoptosis regulator CFLAR <1 647 218233_s_at NM_017601.1 chromosome 6 open reading frame 49 C6orf49 >1 648 214130_s_at AI821791 phosphodiesterase 4D interacting protein (myomegalin) PDE4DIP <1 649 208723_at BC000350.1 ubiquitin specific protease 11 USP11 >1 650 217814_at NM_020198.1 GK001 protein GK001 <1 651 208809_s_at AL136632.1 hypothetical protein FLJ12619 FLJ12619 >1 652 201199_s_at NM_002807.1 proteasome (prosome, macropain) 26S subunit, non-ATPase, 1 PSMD1 <1 653 242937_at AV763408 EST, Moderately similar to ILF1_HUMAN Interleukin enhancer-binding -- >1 factor 1 (Cellular transcription factor ILF-1) [H. sapiens] 654 212333_at AL049943.1 DKFZP564F0522 protein DKFZP564F0522 <1 655 210817_s_at BC004130.1 nuclear domain 10 protein NDP52 <1 656 212508_at AK024029.1 modulator of apoptosis 1 MOAP1 >1 657 213603_s_at BE138888 ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding RAC2 <1 protein Rac2) 658 233274_at AU145144 -- -- >1 659 218557_at NM_020202.1 Nit protein 2 NIT2 <1 660 231428_at BE502947 EST -- <1

Detail Description Table CWU - DETL (20):

NM_018004.1 hypothetical protein FLJ10134 FLJ10134 <1 862 218220_at NM_021640.1 chromosome 12 open reading frame 10 C12orf10 >1 863 213154_s_at AB014599.1 coiled-coil protein BICD2 BICD2 >1 864 200920_s_at AL535380 B-cell translocation gene 1, anti-proliferative BTG1 >1 865 214459_x_at M12679.1 Cw1 antigen HUMMHCW1A <1 866 205955_at NM_018336.1 hypothetical protein FLJ11136 FLJ11136 >1 867 218482_at NM_020189.1 DC6 protein DC6 >1 868 203159_at NM_014905.1 glutaminase GLS <1 869 217823_s_at NM_016021.1 ubiquitin-conjugating enzyme E2, J1 (UBC6 homolog, yeast) UBE2J1 <1 870 225445_at AI332346 EST -- <1 871 211368_s_at U13700.1 caspase 1, apoptosis-related cysteine protease (interleukin 1, beta, convertase) CASP1 <1 872 227811_at AK000004.1 FGD1 family, member 3 FGD3 >1 873 204116_at NM_000206.1 interleukin 2 receptor, gamma (severe combined immunodeficiency) IL2RG <1 874 212120_at BF348067 ras-like protein TC10 TC10 <1 875 37986_at M60459 erythropoietin receptor EPOR <1 876 242692_at AI798758 EST -- >1 877 209644_x_at U38945.1 cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4) CDKN2A >1 878 228545_at AI016784 EST -- <1 879 201858_s_at J03223.1 proteoglycan 1, secretory granule PRG1 <1 880 215823_x_at U64661 EST, Highly similar to PAB1_HUMAN Polyadenylate-binding protein 1 -- >1 (Poly(A)-binding protein 1) (PABP 1) (PABP1) [H. sapiens] 881 201972_at AF113129.1 ATPase, H+ transporting, lysosomal 70 kDa, V1 subunit A, isoform 1 ATP6V1A1 <1 882 201951_at NM_001627.1 activated leukocyte cell adhesion molecule ALCAM <1 883 201986_at NM_005121.1 thyroid hormone receptor-associated protein, 240 kDa subunit TRAP240 <1 884 202393_s_at NM_005655.1 TGFB inducible early growth response TIEG >1 885 212118_at NM_006510.1 ret finger protein RFP <1 886 225910_at BF514723 hypothetical protein LOC284019 LOC284019 <1 887 218795_at NM_016361.1 lysophosphatidic acid phosphatase ACP6 >1 888 204985_s_at NM_024108.1 hypothetical protein MGC2650 MGC2650 >1 889

217436_x_at M80469 -- -- <1 890 215690_x_at AL157437.1 GPAA1P anchor attachment protein 1 homolog (yeast) GPAA1 >1 891 208683_at M23254.1 calpain 2, (m/II) large subunit CAPN2 <1 892 223638_at AL136890.1 hypothetical protein DKFZp434D177 DKFZp434D177 <1 893 218079_s_at NM_024835.1 C3HC4-type zinc finger protein LZK1 <1 894 209250_at BC000961.2 degenerative spermatocyte homolog, lipid desaturase (Drosophila) DEGS <1 895 238724_at R63824 EST -- >1 896 212809_at AA152202 hypothetical protein FLJ14639 FLJ14639 >1 897 222391_at AL080250 hypothetical protein FLJ10856 FLJ10856 <1 898 209533_s_at AF145020.1 phospholipase A2-activating protein PLAA <1 899 218205_s_at NM_017572.1 MAP kinase-interacting serine/threonine kinase 2 MKNK2 >1 900 232174_at AA480392 Homo sapiens clone 24838 mRNA sequence -- >1 901 201068_s_at NM_002803.1 proteasome (prosome, macropain) 26S subunit, ATPase, 2 PSMC2 <1 902 218573_at NM_014061.1 APR-1 protein MAGEH1 <1 903 216272_x_at AF209931.1 hypothetical protein FLJ13511 7h3 >1 904 222309_at AW972292 EST -- >1 905 226461_at AA204719 homeo box B9 HOXB9 >1 906 214449_s_at NM_012249.1 ras-like protein TC10 TC10 <1 907 217880_at AI203880 cell division cycle 27 CDC27 <1 908 213238_at AI478147 ATPase, Class V, type 10D ATP10D <1 909 228464_at AI651510 EST, Weakly similar to T12486 hypothetical protein DKFZp566H033.1 -- -- <1 human [H. sapiens] 910 203157_s_at AB020645.1 glutaminase GLS <1 911 204547_at NM_006822.1 RAB40B, member RAS oncogene family RAB40B >1 912 203067_at NM_003477.1 E3-binding protein PDX1 <1 913 228289_at AI131537 adenylate cyclase 7 ADCY7 <1 914 217955_at NM_015367.1 BCL2-like 13 (apoptosis facilitator) BCL2L13 <1 915 201768_s_at BC004467.1 enthoprotin ENTH <1 916 217832_at NM_006372.1 NS1-associated protein 1 NSAP1 <1 917 226923_at AW205790 hypothetical protein FLJ39514 FLJ39514 <1 918 217939_s_at NM_017657.1 hypothetical protein FLJ20080 FLJ20080 <1 919 244732_at R06827 Homo sapiens, clone IMAGE: 5276307, mRNA -- >1 920 221718_s_at M90360.1 A kinase (PRKA) anchor protein 13 AKAP13 >1 921 218970_s_at NM_015960.1 CGI-32 protein CGI-32 <1 922 214259_s_at AW074911 aldo-keto reductase family 7, member A2 (aflatoxin aldehyde reductase) AKR7A2 >1 923 204020_at BF739943 purine-rich element binding protein A PURA <1 924 205565_s_at NM_000144.1 Friedreich ataxia FRDA <1 925 218768_at NM_020401.1 nuclear pore complex protein NUP107 >1 926 202011_at NM_003257.1 tight junction protein 1 (zona occludens 1) TJP1 <1 927 211423_s_at D85181.1 sterol-C5-desaturase (ERG3 delta-5-desaturase homolog, fungal)-like SC5DL <1 928 202738_s_at BG149218 phosphorylase kinase, beta PHKB <1 929 228697_at AW731710 histidine triad nucleotide binding protein 3 HINT3 <1 930 225317_at AL574669 hypothetical protein MGC2404 MGC2404 >1 931 217368_at X69909 -- -- >1 932 201393_s_at NM_000876.1 insulin-like growth factor 2 receptor IGF2R <1 933 205158_at NM_002937.1 ribonuclease, RNase A family, 4 RNASE4 <1 934 200734_s_at BG341906 ADP-ribosylation factor 3 ARF3 >1 935 239586_at AA085776 hypothetical protein MGC14128 MGC14128 >1 936 225216_at AI590719 Homo sapiens cDNA: FLJ21191 fis, clone COL00104. -- <1 937 203373_at NM_003877.1 suppressor of cytokine signaling 2 SOCS2 >1 938 218003_s_at NM_002013.1 FK506 binding protein 3, 25 kDa FKBP3 >1 939 208296_x_at NM_014350.1 TNF-induced protein GG2-1 <1 940 217716_s_at NM_013336.1 protein transport protein SEC61 alpha subunit isoform 1 SEC61A1 <1 941 202028_s_at BC000603.1 ribosomal protein L38 RPL38 >1 942 218231_at NM_017567.1 N-acetylglucosamine kinase NAGK <1 943 211528_x_at M90685.1 HLA-G histocompatibility antigen, class I, G HLA-G <1 944 203142_s_at NM_003664.1 adaptor-related protein complex 3, beta 1 subunit AP3B1 <1 945 230597_at AI963203 solute carrier family 7 (cationic amino acid transporter, y+ system), member 3 SLC7A3 >1 946 200864_s_at NM_004663.1 RAB11A, member RAS oncogene family RAB11A <1 947 205541_s_at NM_018094.1 G1 to S phase transition 2 GSPT2 <1 948 209267_s_at AB040120.1 BCG-induced gene in monocytes, clone 103 BIGM103 <1 949 207428_x_at NM_001787.1 cell division cycle 2-like 1 (PITSLRE proteins) CDC2L1 >1 950 205801_s_at NM_015376.1

guanine nucleotide exchange factor for Rap1 GRP3 <1 951 228614_at AW182614 hypothetical protein LOC205251 LOC205251 <1 952 230261_at AA552969 Homo sapiens, clone IMAGE: 4816784, mRNA -- <1 953 229194_at AL045882 Homo sapiens, clone IMAGE: 5273745, mRNA -- <1 954 224951_at BE348305 hypothetical protein MGC45411 LOC91012 >1 955 230026_at N74662 mitochondrial ribosomal protein L43 MRPL43 >1 956 217975_at NM_016303.1 pp21 homolog LOC51186 <1 957 212714_at AL050205.1 c-Mpl binding protein LOC113251 <1 958 212990_at AB020717.1 synaptojanin 1 SYNJ1 <1 959 211356_x_at U66495.1 leptin receptor LEPR <1 960 241342_at BG288115 hypothetical protein BC017881 LOC157378 >1 961 239891_x_at AA001052 EST, Weakly similar to RB10_HUMAN Ras-related protein Rab-10 -- <1 [H. sapiens] 962 214672_at AB023215.1 KIAA0998 protein KIAA0998 >1 963 201628_s_at NM_006570.1 Ras-related GTP-binding protein RAGA <1 964 232761_at AL117381 cytochrome c oxidase subunit IV isoform 2 COX4I2 >1 965 233164_x_at AK026955.1 hypothetical protein DKFZp547E052 DKFZp547E052 <1 966 200077_s_at D87914.1 ornithine decarboxylase antizyme 1 OAZ1 >1 967 219549_s_at NM_006054.1 reticulon 3 RTN3 <1 968 203560_at NM_003878.1 gamma-glutamyl hydrolase (conjugase, folylpolygammaglutamyl hydrolase) GGH >1 969 217923_at NM_012392.1 PEF protein with a long N-terminal hydrophobic domain (peflin) PEF <1 970 201862_s_at NM_004735.1 leucine rich repeat (in FLII) interacting protein 1 LRRFIP1 <1 971 223400_s_at AF197569.1 polybromo 1 PB1 <1 972 AFFX- M27830 -- -- >1 M27830_M.sub.-- at 973 41220_at AB023208 MLL septin-like fusion MSF >1 974 209276_s_at AF162769.1 glutaredoxin (thioltransferase) GLRX <1 975 207627_s_at NM_005653.1 transcription factor CP2 TFCP2 <1 976 204785_x_at NM_000874.1 interferon (alpha, beta and omega) receptor 2 IFNAR2 >1 977 222615_s_at AW206812 hypothetical protein FLJ13902 FLJ13902 >1 978 200949_x_at NM_001023.1 ribosomal protein S20 RPS20 >1 979 217192_s_at AL022067 PR domain containing 1, with ZNF domain PRDM1 >1 980 235792_x_at AU154663 Homo sapiens mRNA; cDNA DKFZp564L222 (from clone DKFZp564L222) -- <1 981 213857_s_at BG230614 Homo sapiens, clone IMAGE: 4822825, mRNA -- <1 982 235507_at AA461195 similar to hypothetical protein FLJ10883 LOC115294 >1 983 218191_s_at NM_018368.1 hypothetical protein FLJ11240 FLJ11240 <1 984 200649_at BC002356.1 nucleobindin 1 NUCB1 <1 985 210260_s_at BC005352.1 TNF-induced protein GG2-1 <1 986 209513_s_at BC004331.1 hypothetical protein MGC10940 MGC10940 <1 987 211801_x_at AF329637.1 mitofusin 1 MFN1 <1 988 206875_s_at NM_014720.1 Ste20-related serine/threonine kinase SLK <1 989 39705_at AB014600 SIN3 homolog B, transcriptional regulator (yeast) SIN3B <1 990 203658_at BC001689.1 solute carrier family 25 (carnitine/acylcarnitine translocase), member 20 SLC25A20 <1 991 235566_at AW591660 Homo sapiens cDNA FLJ39046 fis, clone NT2RP7010612. -- <1 992 205089_at NM_003416.1 zinc finger protein 7 (KOX 4, clone HF.16) ZNF7 >1 993 212040_at AK025557.1 Homo sapiens, clone IMAGE: 6057297, mRNA -- <1 994 210962_s_at AB019691.1 A kinase (PRKA) anchor protein (yotiao) 9 AKAP9 <1 995 203053_at NM_005872.1 breast carcinoma amplified sequence 2 BCAS2

Detail Description Table CWU - DETL (31):

s_at protein homeostasis homeostasis 113 200024.sub.-- ribosomal protein S5 RPS5 NR Ribosomes are involved in protein synthesis and thus contribute to Protein at protein homeostasis homeostasis 114 217719.sub.-- eukaryotic translation EIF3S6IP NR Regulates initiation of protein translation and thus is involved in Protein at initiation factor 3, subunit 6 protein homeostasis homeostasis interacting protein 115 225797.sub.-- mitochondrial ribosomal MRPL54 NR involved in mitochondrial protein synthesis Protein at protein L54 homeostasis 116 200937.sub.-- ribosomal protein L5 RPL5 NR Ribosomes are involved in protein synthesis and thus contribute to Protein s_at protein homeostasis homeostasis 117 208985.sub.-- eukaryotic translation EIF3S1 NR Regulates initiation of protein translation and thus is involved in Protein s_at initiation factor 3, protein homeostasis homeostasis subunit 1 alpha,

118 200834.sub.-- 35 kDa ribosomal protein S21 RPS21 NR Ribosomes are involved in protein synthesis and thus contribute to Protein s_at protein homeostasis homeostasis 119 216153.sub.-- reversion-inducing-cysteine- RECK R The protein encoded by this gene is a cysteine-rich, extracellular Tumor x_at rich protein with kazal motifs protein with protease inhibitor-like domains whose expression is Supressor suppressed strongly in many tumors and cells transformed by Pathway various kinds of oncogenes. In normal cells, this membrane- anchored glycoprotein may serve as a negative regulator for matrix metalloproteinase-9, a key enzyme involved in tumor invasion and metastasis. 120 217687.sub.-- adenylate cyclase 2 (brain) ADCY2 R Adenylate cyclase signalling regulates cell growth and Tumor at differentiation; it is frequently defective in human tumors. Supressor Activation of human Adenylyl Cyclase protein(s) and inhibition of Pathway human Pde4 protein protein(s) increase apoptosis of acute lymphoblastic leukemia cells 121 222632.sub.-- leucine zipper transcription LZTFL1 NR The LZTFL1 gene has been mapped to a putative tumor suppressor Tumor s_at factor-like 1 region (C3CER1) on chromosome 3p21.3 Supressor Pathway 122 236623.sub.-- ATPase, Na+/K+ ATP1A1 R Expression regulated by p53, a tumor supressor gene Tumor at transporting, alpha 1 Supressor polypeptide Pathway 123 221899.sub.-- hypothetical protein from CG005 R Located in the region of BRCA2, a breast cancer susceptibility gene Tumor at BCRA2 region Supressor Pathway 124 221691.sub.-- nucleophosmin (nucleolar NPM1 NR Nucleophosmin regulates the stability and transcriptional activity of Tumor x_at phosphoprotein B23, p53 Supressor numatrin) Pathway 125 209030.sub.-- immunoglobulin superfamily, IGSF4 NR TSCL1 has been identified as a potential tumor supressor gene in Tumor s_at member 4 (TSLC1) lung cancer Supressor Pathway 126 222762.sub.-- LIM domains containing 1 LIMD1 NR Interstitial deletions of the short arm of chromosome 3 containing Tumor x_at (LIMD1) LILMD1 are found in a large number of tumors. IT may have a role Supressor as a tumor supressor. Pathway 127 240983.sub.-- cysteinyl-tRNA synthetase CARS NR This gene is one of several located near the imprinted gene domain Tumor s_at of 11p15.5, an important tumor-suppressor gene region. Alterations Supressor in this region have been associated with the Beckwith-Wiedemann Pathway syndrome, Wilms tumor, rhabdomyosarcoma, adrenocortical carcinoma, and lung, ovarian, and breast cancer. 128 200713.sub.-- microtubule-associated MAPRE1 NR MAPRE1 binds to the APC protein which is often mutated in Tumor s_at protein, RP/EB family, familial and sporadic forms of colorectal cancer. This protein Supressor member 1 localizes to microtubules, especially the growing ends, in interphase Pathway cells. During mitosis, the protein is associated with the centrosomes and spindle microtubules. 129 200814.sub.-- proteasome (prosome, PSME1 NR subunit of the 11S regulator of the 20S proteasome Ubiquitin/ at macropain) activator subunit 1 proteasome (PA28 alpha) pathway 130 201532.sub.-- proteasome (prosome, PSMA3 NR core subunit of the proteasome Ubiquitin/ at macropain) subunit, proteasome alpha type, 3 pathway 131 218011.sub.-- ubiquitin-like 5 UBL5 NR Ubiquitin-like proteins (UBLs) are thought to be reversible Ubiquitin/ at modulators of protein function rather than protein degraders like proteasome ubiquitin pathway 132 224747.sub.-- hypothetical protein L0C92912 NR Contains a ubiquitin conjugating enzyme domain Ubiquitin/ at LOC92912 proteasome pathway 133 201758.sub.-- tumor susceptibility gene 101 TSG101 NR The protein encoded by this gene belongs to a group of apparently Ubiquitin/ at inactive homologs of ubiquitin-conjugating enzymes. The gene proteasome product contains a coiled-coil domain that interacts with stathmin, a pathway cytosolic phosphoprotein implicated in tumorigenesis. The protein may play a role in cell growth and differentiation and act as a negative growth regulator. 134 200019.sub.-- Finkel-Biskis-Reilly murine FAU NR A fusion protein consisting of the ubiquitin-like protein fubi at the Ubiquitin/ s_at sarcoma virus (FBR-MuSV) N terminus and ribosomal protein S30 at the C terminus. It has been proteasome ubiquitously expressed (fox proposed that the fusion protein is post-translationally processed to pathway derived);

ribosomal protein generate free fubi and free ribosomal protein S30. Fubi is a member S30 of the ubiquitin family, and ribosomal protein S30 belongs to the S30E family of ribosomal proteins. 135 202346.sub.-- huntingtin interacting HIP2 NR UBIQUITIN-CONJUGATING ENZYME E2-25 K has been Ubiquitin/ at protein 2 implicated in the degradation of huntingtin and suppression of proteasome apoptosis. pathway 136 201177 SUMO-1 activating enzyme UBA2 NR ubiquitin-like activating enzyme involved in protein homeostasis Ubiquitin/ s_at subunit 2 proteasome pathway 154 218438.sub.-- endothelial-derived gene 1 EG1 NR expressed in tumor-stimulated endothelial cells; may have role in s_at tumor angiogenesis 157 216288.sub.-- cysteinyl leukotriene CYSLTR1 R upregulated in colon cancer; affecting survival at receptor 1 166 210497.sub.-- synovial sarcoma, SSX2 NR A cancer antigen involved in a translocation in synovial sarcoma. x_at X

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DOCUMENT-IDENTIFIER: US 20040110221 A1

TITLE: Methods for diagnosing RCC and other solid tumors

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INVENTOR-INFORMATION:

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ABSTRACT:

Methods, systems and equipment for diagnosing renal cell carcinoma (RCC) and other solid tumors. This invention identifies numerous disease genes that are differentially expressed in the peripheral blood of patients having RCC or other solid tumors relative to disease-free humans. These disease genes can be used as surrogate markers for detecting the presence or absence of RCC or other solid tumors.

[0001] This application incorporates by reference the entire disclosure of U.S. Provisional Application Serial No. 60/427,982, filed Nov. 21, 2002 and entitled "Methods for Diagnosing RCC and/or Solid Tumors." This application also incorporates by reference the entire disclosure of U.S. Provisional Application Serial No. 60/459,782, filed Apr. 3, 2003 and entitled "Methods for Diagnosing RCC and/or Solid Tumors." In addition, this application incorporates by reference all materials recorded in compact discs "Copy 1" and "Copy 2." Each of the compact discs includes the sequence listing file entitled "AM101080L Sequence Listing.ST25.txt" (2,206 KB, created on Nov. 20, 2003).

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Detail Description Paragraph - DETX (187):
[0224] CPS 105 corresponds to CDC34 which encodes cell division cycle 34. The gene has LocusID: 997, and is located on chromosome 19 with reported

cytogenetic location 19p13.3. The protein encoded by this gene is a member of the ubiquitin conjugating enzyme family. Ubiquitin-conjugating enzyme catalyzes the covalent attachment of ubiquitin to other proteins. CDC34 gene product may be a part of the large multiprotein complex, which is involved in ubiquitin-mediated degradation of cell cycle G1 regulators and the initiation of DNA replication. The gene product is similar to S. cerevisiae Cdc34p, and may covalently attach ubiquitin to substrate proteins.

Detail Description Table CWU - DETL (7):

3TABLE 3 SEQ ID NOs and the Corresponding Entrez Accession Numbers Corresponding SEQ ID Entrez Database NO Accession No. Reported Source of the Corresponding Entrez Sequence 1 AF051152 Homo sapiens Toll/interleukin-1 receptor-like protein 4 (TIL4) mRNA 2 AA978353 3 AB006780 Homo sapiens mRNA for galectin-3 4 AB013382 Homo sapiens mRNA for DUSP6 6 U66359 Human T54 protein (T54) mRNA 7 X75593 Homo sapiens mRNA for rab 13 8 X91348 Homo sapiens predicted non coding cDNA (DGCR5) 9 L35240 Human enigma gene 10 AF017257 Homo sapiens chromosome 21 derived BAC containing erythroblastosis virus oncogene homolog 2 protein (ets-2) gene 11 AB011161 Homo sapiens mRNA for KIAA0589 protein 12 D43642 Human YL-1 mRNA for YL-1 protein (nuclear protein with DNA-binding ability) 13 AF055000 Homo sapiens clone 24519 unknown mRNA 14 AB006537 Homo sapiens mRNA for interleukin 1 receptor accessory protein 15 X75042 Homo sapiens rel proto-oncogene mRNA 16 AF032108 Homo sapiens integrin alpha-7 mRNA 17 L07592 Human peroxisome proliferator activated receptor mRNA 18 X52015 Homo sapiens mRNA for interleukin-1 receptor antagonist 19 AF025533 Homo sapiens leukocyte immunoglobulin-like receptor-3 (LIR-3) mRNA 21 U05770 Human annexin V (ANX5) gene, exon 13 22 W26700 23 AF052111 Homo sapiens clone 23953 mRNA sequence 24 M64925 Human palmitoylated erythrocyte membrane protein (MPP1) mRNA 25 M19267 Human tropomyosin mRNA 26 M62896 Human lipocortin (LIP) 2 pseudogene mRNA 27 M13207 Human granulocyte-macrophage colony-stimulating factor (CSF1) gene 28 D86961 Human mRNA for KIAA0206 gene 29 AA187563 30 J05581 Human polymorphic epithelial mucin (PEM) mRNA 31 AF035819 Homo sapiens macrophage receptor MARCO mRNA 32 X51362 Human mRNA for dopamine D2 receptor 33 AA844998 34 AB008775 Homo sapiens AQP9 mRNA for aquaporin 9 35 AB000520 Homo sapiens mRNA for APS 36 X60364 Human ALAS mRNA for 5-aminolevulinate synthase precursor 37 X12451 Human mRNA for pro-cathepsin L (major excreted protein MEP) 38 AL080235 Homo sapiens mRNA; cDNA DKFZp586E1621 (from clone DKFZp586E1621) 40 D32143 Human mRNA for biliverdin-IXbeta reductase I 41 L22075 Homo sapiens guanine nucleotide regulatory protein (G13) mRNA 42 D87116 Human mRNA for MAP kinase kinase 3b 43 AA135683 44 AF079221 Homo sapiens BCL2/adenovirus E1B 19 kDa- interacting protein 3a mRNA 45 U48213 Human D-site binding protein gene, exon 4 46 U91316 Human acyl-CoA thioester hydrolase mRNA 47 AF059202 Homo sapiens ACAT related gene product 1 mRNA 48 L76200 Human guanylate kinase (GUK1) mRNA 49 L42243 Homo sapiens (clone 51H8) alternatively spliced interferon receptor (IFNAR2) gene, exon 9 50 D45421 Human mRNA for phosphodiesterase I alpha 51 AL096737 Homo sapiens mRNA; cDNA DKFZp434F152 (from clone DKFZp434F152) 52 L32831 Homo sapiens G protein-coupled receptor (GPR3) gene 53 X07834 Human mRNA for manganese superoxide dismutase (EC 1.15.1.1) 54 AJ243797 Homo sapiens mRNA for deoxyribonuclease III (drn3 gene) 55 H12458 56 S78798 1-phosphatidylinositol-4-phosphate 5-kinase isoform C [human, peripheral blood leukocytes, mRNA, 1835 nt] 57 M94856 Human fatty acid binding protein homologue (PA- FABP) mRNA 58 J05070 Human type IV collagenase mRNA 59 J04027 Human plasma membrane Ca2+ pumping ATPase mRNA 60 U43843 Human h-neuro-d4 protein mRNA 61 D10925 Human mRNA for HM145 62 AJ000480 Homo sapiens mRNA for C8FW phosphoprotein 63 M25915 Human complement cytolysis inhibitor (CLI) mRNA 64 D30783 Homo sapiens mRNA for epiregulin 65 AF017786 Homo sapiens phosphatidic acid phosphohydrolase homolog (Dri42) mRNA 66 X79535 Homo sapiens mRNA for beta tubulin, clone nuk_278 67 D14689 Human mRNA

for KIAA0023 gene 68 AL031230 Human DNA sequence from clone 73M23 on chromosome 6p22.2-22.3; contains the 5' part of the possibly alternatively spliced gene for Phosphatidylinositol-gly- can-specific Phospholipase D 1 precursor (EC 3.1.4.50, PIGPLD1, Glycoprotein Phospholipase D, Glycosyl-Phosphatidylinositol specific Phospholipase D), the gene for NAD+-dependent succinic semialdehyde dehydrogenase (SSADH, EC 1.2.1.24), and the 3' part of the KIAA0319 gene; contains ESTs, STSs, GSSs and a putative CpG island, complete sequence 69 AL049963 Homo sapiens mRNA; cDNA DKFZp564A132 (from clone DKFZp564A132) 70 Z32684 Homo sapiens mRNA for membrane transport protein (XK gene) 71 AB020644 Homo sapiens mRNA for KIAA0837 protein 72 X12496 Human mRNA for erythrocyte membrane sialoglycoprotein beta (glycophorin C) 73 L23959 Homo sapiens E2F-related transcription factor (DP-1) mRNA 74 U61836 Human putative cyclin G1 interacting protein mRNA 75 U43774 Human Fc alpha receptor, splice variant FcalphaR a.2 (CD89) mRNA 76 M35999 Human platelet glycoprotein IIIa (GPIIIa) mRNA 77 L07648 Human MXI1 mRNA 78 M24069 Human DNA-binding protein A (dbpA) gene, 3' end 79 AF061034 Homo sapiens FIP2 alternatively translated mRNA 80 U29091 Homo sapiens selenium-binding protein (hSBP) mRNA 81 U68111 Human protein phosphatase inhibitor 2 (PPP1R2) gene, exon 6 82 X82460 Homo sapiens mRNA for 15-hydroxy prostaglandin dehydrogenase 84 U58917 Homo sapiens IL-17 receptor mRNA 85 AB010419 Homo sapiens mRNA for MTG8-related protein MTG16a 86 AB007943 Homo sapiens mRNA for KIAA0474 protein 87 Z23115 Homo sapiens bcl-xL mRNA 88 AF001461 Homo sapiens Kruppel-like zinc finger protein Zf9 mRNA 89 D14874 Homo sapiens mRNA for adrenomedullin precursor 90 J05500 Human beta-spectrin (SPTB) mRNA 91 M34480 Human platelet glycoprotein IIb (GPIIb) mRNA 92 U97067 Homo sapiens alpha-catenin-like protein mRNA 93 M26683 Human interferon gamma treatment inducible mRNA 94 AA527880 95 X72308 Homo sapiens mRNA for monocyte chemotactic protein-3 (MCP-3) 96 M63835 Human IgG Fc receptor I gene, exon 6 97 U28389 Human dematin 52 kDa subunit mRNA 98 U21049 Homo sapiens DD96 mRNA 99 L40904 Homo sapiens peroxisome proliferator activated receptor gamma (PPARG) mRNA 100 AI961220 101 X74039 Homo sapiens mRNA for urokinase plasminogen activator receptor 102 L22005 Human ubiquitin conjugating enzyme mRNA 103 AI732885 104 U00672 Human interleukin-10 receptor mRNA 105 AL050254 Novel human gene mapping to chomosome 22 106 AF026939 Homo sapiens CIG49 (cig49) mRNA 107 U19599 Human (BAX delta) mRNA 108 X64364 Homo sapiens mRNA for M6 antigen 109 U12471 Human thrombospondin-1 gene 110 AF068706 Homo sapiens gamma2-adaptin (G2AD) mRNA 111 L42542 Human RLIP76 protein mRNA 112 AF070587 Homo sapiens clone 24741 mRNA sequence 113 AJ001481 Homo sapiens mRNA for DUX1 protein 114 U36341 Human Xq28 cosmid, creatine transporter (SLC6A8) gene, complete

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DOCUMENT-IDENTIFIER: US 20040110215 A1

TITLE: Human proteins responsible for NEDD8 activation and conjugation

PUBLICATION-DATE: June 10, 2004

INVENTOR-INFORMATION:

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US-CL-CURRENT: 435/6, 435/226 , 435/320.1 , 435/325 , 435/69.1 , 530/388.26 , 536/23.2

ABSTRACT:

The invention relates to covalent modification of proteins through their conjugation with other proteins. More particularly, the invention relates to the modulation of such conjugation involving the protein NEDD8. The invention provides compositions and methods for detecting and/or modulating the activation and/or conjugation of NEDD8, as well as compositions and methods for discovering molecules which are useful in detecting and/or modulating the activation and/or conjugation of NEDD8. The present invention arises from the purification and characterization of novel NEDD8 activating and conjugating enzymes.

[0001] This application is a continuation-in-part of provisional application Serial No. 60/068,209, filed 19 Dec. 1997, and a continuation-in-part of provisional application Serial No. 60/096,525, filed 12 Aug. 1998.

---------- KWIC ---------

Brief Description of Drawings Paragraph - DRTX (8):

[0045] FIG. 7 shows the sequence alignment of NCE1 and NCE2 with known Ubc proteins.

Detail Description Paragraph - DETX (76):

[0109] The putative human homolog of yeast Ubc12 was identified by searching the human EST database for clones having coding sequences that are homologous to the yeast protein. An initial search using the yeast protein sequence identified several clones. Clone AA261836, which contains a coding sequence very similar to a region of the yeast protein was used to search for further EST clones. The search led to the construction of a contiguous consensus sequence from overlapping clones which predicts a gene to encode a protein having 183 amino acids, with a predicted molecular mass of 20899 Da. The contiguous nucleotide sequence was obtained using nested PCR on a human leukocyte cDNA library. The first PCR used primers having the sequence GCAGGATGATCAAGCTGTTCTCGC (forward) and CGTGGCGGGGGTGGGTATGCGCCA (reversed). The second PCR used the primers CGGGAATTCCATATGATCAAGCTGTTCTCGCTG (forward) and CGCCCAAGCTTCTATTTCAGGCAGCGCTCAAAG (reversed). The PCR product was digested with Nde1 and HindIII and ligated with similarly digested plasmid pT7-7. The resulting clone, pT7-7-UbcH12, was sequenced to determine the nucleotide sequence [SEQ ID NO 3] and deduced amino acid sequence [SEQ ID NO 4] shown in FIG. 1. FIG. 2 shows the alignment of NCE1 with yeast Ubc12. NCE1 shows 41% identity and 63% homology with yeast Ubc12.

Detail Description Paragraph - DETX (85):

[0112] The human EST database was searched using as query sequence HPNITETICLSLLREHSIDGTGWA. This is the sequence of clone AA306113 and bears similarity to the active site of proteins in the UBC protein family. Clones were identified which had sequences overlapping the sequence of clone AA306113. The identified sequences of the overlapping EST clones were aligned by the program CLUSTALW (See Thompson et al., Nucleic Acids Res. 22: 4673-4680 (1994), or by the program SeqMan (DNASTAR, Inc., Madison, Wis.) to yield a consensus sequence, CON1. CON 1 was used to perform searches for additional clones with overlapping sequences. The overlapping sequences yielded an open reading frame which encodes a protein of 185 amino acids (predicted molecular mass=21076 Da). Based upon homology to known human Ubc proteins, this gene is a member of the human Ubc gene family. The contiguous nucleotide sequence of NCE2 was obtained using nested PCR on a human leukocyte cDNA library. The first PCR used the primers AGCCCAGGGTAAAGGCAGCA (forward) and CATGTTAGAGACAAACTGTA (reversed). The second PCR used the primers GGGAATTCCATATGCTAACGCTAGCAAGTAA (forward) and CCATCGATTCATCTGGCATAACGTTTG- A (reversed). The PCR product was then cloned into the NdeI/HindIII sites of pT7-7 to generate the plasmid pT7-7-HSUBC17. The sequence of the NCE2 gene and its deduced amino acid sequence are shown in FIG. 4. No close homolog exists in the yeast genome. The protein has 46% identity and 64% homology with a C. elegans gene (Genebank Accession # CE 275850) of unknown function (see FIG. 5).

Detail Description Paragraph - DETX (94):

[0115] The active site cysteine of a cloned NCE1 or NCE2 is assigned by examining the sequence alignment with known Ubc proteins (see FIG. 6 for alignment). The active site cysteine is replaced by a serine using standard site-specific mutagenesis. The mutant protein is expressed in bacteria and purified. The ability of the mutant protein to form a stable oxygen ester with NEDD8 is established as described in Examples 8 and 11 above, except that the bond formation is not labile in DTT. Dominant negative mutant activity is then established by introducing the mutant protein in increasing concentrations in an assay as described in Examples 8 and 11 above and demonstrating dose-dependent inhibition of NEDD8/NCE1 or NCE2 complex formation.

PGPUB-DOCUMENT-NUMBER: 20040102400

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040102400 A1

TITLE: Modulation of UBE2G1 expression

PUBLICATION-DATE: May 27, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Bennett, C. Frank	Carlsbad	CA	US	
Dean, Nicholas M.	Olivenhain	CA	US	
Dobie, Kenneth W.	Del Mar	CA	US	

APPL-NO: 10/ 303587

DATE FILED: November 21, 2002

US-CL-CURRENT: 514/44, 536/23.5

ABSTRACT:

Compounds, compositions and methods are provided for modulating the expression of UBE2G1. The compositions comprise oligonucleotides, targeted to nucleic acid encoding UBE2G1. Methods of using these compounds for modulation of UBE2G1 expression and for diagnosis and treatment of disease associated with expression of UBE2G1 are provided.

---------- KWIC --------

Summary of Invention Paragraph - BSTX (5):

[0003] One member of the E2 family, UBE2G1, is a ubiquitin conjugating enzyme strongly expressed in skeletal muscle and may therefore have a unique role in muscle-specific protein degradation (Watanabe et al., Cytogenet. Cell Genet., 1996, 74, 146-148). The gene encoding UBE2G1 (also called UBE2G and ubiquitin-conjugating enzyme E2G) was cloned in 1996 (Watanabe et al., Cytogenet. Cell Genet., 1996, 74, 146-148). The UBE2G1 protein has 74% identity at the amino acid level with UBC7 of C. elegans and significant homology with yeast UBC7, a protein which confers resistance to cadmium poisoning. Transcripts of three sizes were detected in skeletal muscle and weak expression was observed in other tissues. Disclosed and claimed in U.S. Pat. No. 6,166,190 is an isolated nucleic acid encoding human UBE2G1 (Tsutomu and Watanabe, 2000). The expression of several components of the ubiquitin pathway, including UBE2G1, is regulated by insulin-like growth factor I (IGF-I) during catabolism, suggesting a mechanism for the anti-proteolytic actions of IGF-I and a link between IGF-I and cellular events resulting from proteolysis via the ubiquitin pathway (Chrysis and Underwood, Endocrinology, 1999, 140, 5635-5641).

PGPUB-DOCUMENT-NUMBER: 20040102394

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040102394 A1

TITLE: Modulation of huntingtin interacting protein 2 expression

PUBLICATION-DATE: May 27, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Bennett, C. Frank	Carlsbad	CA	US	
Dean, Nicholas M.	Olivenhain	CA	US	
Dobie, Kenneth W.	Del Mar	CA	US	

APPL-NO: 10/ 303292

DATE FILED: November 23, 2002

US-CL-CURRENT: 514/44, 536/23.5

ABSTRACT:

Compounds, compositions and methods are provided for modulating the expression of huntingtin interacting protein 2. The compositions comprise oligonucleotides, targeted to nucleic acid encoding huntingtin interacting protein 2. Methods of using these compounds for modulation of huntingtin interacting protein 2 expression and for diagnosis and treatment of disease associated with expression of huntingtin interacting protein 2 are provided.

---------- KWIC --------

Summary of Invention Paragraph - BSTX (6):

[0004] Huntingtin interacting protein 2 is one member of the E2 family of ubiquitin-conjugating enzymes and has been shown to interact with huntingtin, the protein which upon mutation is responsible for the development of Huntington's disease. The gene encoding huntingtin interacting protein 2 (also called HIP2, HIP-2, E2-25K, low density lipoprotein-inducible gene, and LIG) was cloned in 1996 (Kalchman et al., J. Biol. Chem., 1996, 271, 19385-19394) and potential splice variants have been noted (Kikuchi et al., Arterioscler. Thromb. Vasc. Biol., 2000, 20, 128-134). Huntingtin interacting protein 2 shares complete homology with the bovine E2-25K enzyme, placing it in the same class of E2 enzymes encoded by UBC1, UBC4, and UBC5 genes of S. cerevisiae (Kalchman et al., J. Biol. Chem., 1996, 271, 19385-19394). Huntingtin interacting protein 2 is expressed in most human tissues (Kalchman et al., J. Biol. Chem., 1996, 271, 19385-19394), including human fetal membranes during distention (Nemeth et al., Am. J. Obstet. Gynecol., 2000, 182, 60-67).

US-PAT-NO: 6881571

DOCUMENT-IDENTIFIER: US 6881571 B1

TITLE: Qualitative differential screening

DATE-ISSUED: April 19, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Schweighoffer; Fabien	Vincennes	N/A	N/A	FR
Bracco; Laurent	Paris	N/A	N/A	FR
Tocque; Bruno	Courbevoie	N/A	N/A	FR

APPL-NO: 09/ 623828

DATE FILED: November 30, 2000

PARENT-CASE:

This application is continuation-in-part of U.S. Ser. No. 09/046,920, filed Mar. 24, 1998, now U.S. Pat. No. 6,251,590.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
FR	98 02997	March 11, 1998

PCT-DATA:
APPL-NO: PCT/FR99/00547
DATE-FILED: March 11, 1999
PUB-NO: WO99/46403
PUB-DATE: Sep 16, 1999
371-DATE: Nov 30, 2000
102(E)-DATE:Nov 30, 2000

US-CL-CURRENT: 435/287.2, 435/6 , 435/7.1 , 435/91.1 , 435/91.2 , 536/22.1 , 536/23.1 , 536/24.3 , 536/24.31 , 536/24.32 , 536/24.33

ABSTRACT:

The invention concerns a method for identifying and/or cloning nucleic acid regions representing qualitative differences associated with alternative splicing events and/or with insertions, deletions located in RNA transcribed genome regions, between two physiological situations, comprising either hybridization of RNA derived from the test situation with cDNA's derived from the reference situation and/or reciprocally, or double-strand hybridization of cDNA derived from the test situation with cDNA's derived from the reference situation; and identifying and/or cloning nucleic acids representing qualitative differences. The invention also concerns compositions or banks of nucleic acids representing qualitative differences between two physiological situations, obtainable by the above method, and their use as probe, for identifying genes or molecules of interest, or still for example in methods of pharmacogenomics, and profiling of molecules relative to their therapeutic and/or toxic effects. The invention further concerns the use of dysregulation of splicing RNA as markers for predicting molecule toxicity and/or efficacy, and as markers in pharmacogenomics.

22 Claims, 26 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 26

---------- KWIC ---------

Other Reference Publication - OREF (3):
Ardley, et al., "Rapid isolation of genomic clones for individual members of human multigene families: Identification and localisation of UBE2L4, a novel member of a ubiquitin conjugating enzyme dispersed gene family" Cytogenetics and Cell Genetics, 79:188-192 (1997).

US-PAT-NO: 6794137

DOCUMENT-IDENTIFIER: US 6794137 B2
See image for Certificate of Correction

TITLE: Gene markers useful for detecting skin damage in response to ultraviolet radiation

DATE-ISSUED: September 21, 2004

US-CL-CURRENT: 435/6, 536/23.1 , 536/24.3

APPL-NO: 09/ 947870

DATE FILED: September 6, 2001

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/231,454, filed Sep. 8, 2000.

US-PAT-NO: 6750027

DOCUMENT-IDENTIFIER: US 6750027 B2

TITLE: Human ubiquitin-conjugating enzyme homologs

DATE-ISSUED: June 15, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lal; Preeti	Sunnyvale	CA	N/A	N/A
Hillman; Jennifer L.	Mountain View	CA	N/A	N/A
Guegler; Karl J.	Menlo Park	CA	N/A	N/A
Corley; Neil C.	Mountain View	CA	N/A	N/A
Azimzai; Yalda	Union City	CA	N/A	N/A

APPL-NO: 09/ 930026

DATE FILED: August 14, 2001

PARENT-CASE:

This application is a divisional application of U.S. application Ser. No. 09/058,368 filed on Apr. 9, 1998, now U.S. Pat. No. 6,277,568, entitled NUCLEIC ACIDS ENCODING HUMAN UBIQUITIN-CONJUGATING ENZYME HOMOLOGS, the contents of which are hereby incorporated by reference.

US-CL-CURRENT: 435/7.1, 435/183 , 435/193 , 435/4 , 435/7.4 , 436/501 , 530/350

ABSTRACT:

The invention provides human ubiquitin-conjugating enzyme homologs (UCEH) and polynucleotides which identify and encode UCEH. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating or preventing disorders associated with expression of UCEH.

10 Claims, 0 Drawing figures

Exemplary Claim Number: 1

---------- KWIC ---------

Abstract Text - ABTX (1):

The invention provides human ubiquitin-conjugating enzyme homologs (UCEH) and polynucleotides which identify and encode UCEH. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating or preventing disorders associated with expression of UCEH.

TITLE - TI (1):

Human ubiquitin-conjugating enzyme homologs

Parent Case Text - PCTX (1):

This application is a divisional application of U.S. application Ser. No.

09/058,368 filed on Apr. 9, 1998, now U.S. Pat. No. 6,277,568, entitled NUCLEIC ACIDS ENCODING HUMAN UBIQUITIN-CONJUGATING ENZYME HOMOLOGS, the contents of which are hereby incorporated by reference.

Brief Summary Text - BSTX (2):
This invention relates to nucleic acid and amino acid sequences of human ubiquitin-conjugating enzyme homologs and to the use of these sequences in the diagnosis, treatment, and prevention of cancer, autoimmune disorders, and neuronal disorders.

Brief Summary Text - BSTX (5):
Substrate recognition by this pathway involves a specialized recognition and targeting apparatus, known as the ubiquitin-conjugating system. Ubiquitin-conjugating enzyme (E2) and ubiquitin-protein ligase (E3), either independently or in conjunction, catalyze isopeptide formation between the carboxyl terminus of ubiquitin and amino groups of internal lysine residues of target proteins. (Scheffner M. et al. (1995) Nature 373: 81-83.) Ubiquitin-protein conjugates are then recognized and degraded by a specific protease complex, the 26S proteasome. Both E2 and E3 exist as protein families, and their pattern of expression is thought to determine substrate specificity. (Nuber U. et al. (1996) J. Biol. Chem. 271: 2795-2800.) For example, E6 oncoprotein of the cancer-associated human papillomavirus types 16 and 18, inactivates the tumor suppressor protein p53 via the ubiquitin protein degradation pathway. An E3 protein, E6-AP, and an E2 protein, either UbcH5 or UbcH7, complex with E6 and specifically conjugate ubiquitin to p53. (Scheffner M. et al. (1993) Cell 75: 495-505; Nuber et al., supra.) Other E2 proteins are not sufficient for p53 ubiquitination, thus UbcH5 and UbcH7 appear to be involved in the specific targeting of p53 for degradation.

Brief Summary Text - BSTX (11):
The discovery of new human ubiquitin-conjugating enzyme homologs and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, treatment, and prevention of cancer, autoimmune disorders, and neuronal disorders.

Brief Summary Text - BSTX (13):
The invention features substantially purified polypeptides, human ubiquitin-conjugating enzymes, referred to collectively as "UCEH" and individually as "UCEH-1," "UCEH-2," and "UCEH-3." In one aspect, the invention provides a substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, a fragment of SEQ ID NO:1, a fragment of SEQ ID NO:2, and a fragment of SEQ ID NO:3.

Detailed Description Text - DETX (52):
In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:2. UCEH-2 is 282 amino acids in length and has an ubiquitin-conjugating enzyme active site signature sequence from W.sub.82 through I.sub.96. In addition, UCEH-2 has a potential N-glycosylation site at residue N.sub.201, a potential glycosaminoglycan attachment site at S.sub.273, five potential casein kinase II phosphorylation sites at residues S.sub.19, T.sub.31, T.sub.51, T.sub.172, and T.sub.186, three potential protein kinase C phosphorylation sites at S9, T.sub.74, and S.sub.111, and two potential tyrosine kinase phosphorylation sites at Y.sub.70 and Y.sub.b 161. PFAM analysis identifies UCEH-2 as an ubiquitin-conjugating enzyme (UQ_con) with the region from residue 5 through 167 receiving a score of 264 bits. BLOCKS analysis also identifies UCEH-2 as an ubiquitin-conjugating enzyme (BL00183), with the region from residue 41 through 93 receiving a score of 1473 and a strength of 1512. BLAST analysis indicates that UCEH-2 has chemical and

structural similarity with Oryctolagus cuniculus ubiquitin-conjugating enzyme E2 (GI 1381181). Northern analysis shows the expression of SEQ ID NO:5 in various libraries, at least 47% of which are immortalized or cancerous and at least 29% of which involve immune response. In addition, 31% of the libraries showing expression of UCEH-2 were from reproductive tissue, and 15% were from gastrointestinal tissue. Of particular note is the expression of UCEH-2 in tumors of the colon and breast. A fragment of SEQ ID NO:5 from about nucleotide 480 to about nucleotide 540 is useful, e.g., as a hybridization probe.

Other Reference Publication - OREF (5):
Nuber, U., et al., "Cloning of Human Ubiquitin-conjugating Enzymes UbcH6 and UbcH7 (E2-F1) and Characterization of Their Interaction with E6-AP and RSP5," Journal of Biol. Chem., 271(5):2795-2800 (1996).

US-PAT-NO: 6747128

DOCUMENT-IDENTIFIER: US 6747128 B2

TITLE: Components of ubiquitin ligase complexes, and uses related thereto

DATE-ISSUED: June 8, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Caligiuri; Maureen	Reading	MA	N/A	N/A
Rolfe; Mark	Newton	MA	N/A	N/A

APPL-NO: 08/ 915048

DATE FILED: August 20, 1997

US-CL-CURRENT: 530/350, 435/183 , 435/219 , 435/252.3 , 435/254.11 , 435/320.1 , 435/325 , 536/23.1 , 536/23.2 , 536/23.5

ABSTRACT:

The present invention relates to the isolation of a new class of ubiquitin ligases involved in protein degradation in vertebrate organisms, such as protein degradation of cell cycle regulatory proteins. Accordingly, the invention provides nucleic acids and the proteins encoded by said nucleic acids which play a role in the ubiquitinylation and subsequent degradation of substrate proteins and in regulating cell proliferation, cell differentiation, and cell survival. The invention also provides methods for modulating protein degradation, cell proliferation, cell differentiation and/or cell survival by modulating protein ubiquitination; assays for identifying compounds which modulate protein degradation, cell proliferation, differentiation and/or cell survival; methods for treating disorders associated with aberrant protein degradation, cell proliferation, cell differentiation, and/or cell survival; and diagnostic and prognostic assays for determining whether a subject is at risk of developing a disorder associated with an aberrant protein degradation, cell proliferation, cell differentiation, and/or survival.

18 Claims, 0 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 2

---------- KWIC ---------

Detailed Description Text - DETX (7):

It has been reported that, both in vivo and in vitro, p27 is found to be degraded by the ubiquitin-dependent proteasome pathway. For instance, the human ubiquitin-conjugating enzymes Ubc2 and Ubc3 were shown to be involved in the ubiquitination of p27. Compared with proliferating cells, quiescent cells exhibited a smaller amount of p27 ubiquitinating activity, which accounted for the marked increase of p27 half-life measured in these cells. Thus, the abundance of p27 in cells is regulated by degradation. The specific proteolysis of p27 may represent a mechanism for regulating the activity of

cyclin-dependent kinases. See, Pagano et al. (1995) Science 269: 682-685, and PCT publication WO 94/18974.

Detailed Description Text - DETX (91):

In general, the biological activity of a SIP polypeptide will be characterized as including the ability, in the presence of other required proteins, to mediate and/or catalyze the transfer a ubiquitin molecule from a relevant ubiquitin conjugating enzyme (UBC) to a lysine residue of its substrate protein. The above notwithstanding, the biological activity of a SIP polypeptide may be characterized by one or more of the following attributes: an ability to regulate the cell-cycle of an eukaryotic cell, especially a mammalian cell (e.g., of a human cell), or a yeast cell such as a Schizosaccharomyces cell; an ability to modulate proliferation/cell growth of a eukaryotic cell; an ability to modulate entry of a mammalian or yeast cell into S phase; an ability to ubiquitinate a cell-cycle regulator, e.g. a cyclin dependent kinase inhibitor, e.g., p27. The SIP polypeptides of the present invention may also function to modulate differentiation of cells/tissue. The subject polypeptides of this invention may also be capable of modulating cell growth or proliferation by influencing the action of other cellular proteins. A SIP polypeptide can be a specific agonist of the function of the wild-type form of the protein, or can be a specific antagonist, such as a catalytically inactive mutant. Other biological activities of the subject SIP proteins are described herein, or will be reasonably apparent to those skilled in the art in light of the present disclosure.

Detailed Description Text - DETX (95):

Fragments of the nucleic acid encoding a biologically active portion of the subject SIP proteins are also within the scope of the invention. As used herein, a fragment of the nucleic acid encoding an active portion of a SIP protein refers to a nucleotide sequence having fewer nucleotides than the nucleotide sequence encoding the full length amino acid sequence of, for example, the SIP protein represented in SEQ ID NO: 2, and which encodes a polypeptide which retains at least a portion of the biological activity of the full-length protein as defined herein, or alternatively, which is functional as an antagonist of the biological activity of the full-length protein. For example, such fragments include, as appropriate to the full-length protein from which they are derived, a polypeptide containing a domain mediating the interaction of the SIP protein with another protein. For example, a biologically active portion of a SIP ligase can be a portion of a cdc4 protein of the invention which is capable of interacting with a cullins protein, with a ubiquitin conjugating enzyme, with a skpl protein and/or with a substrate protein. Particularly preferred biologically active portions of vertebrate SIP proteins of the invention include the WD repeats, which are located between approximately residues 642-1073 of SEQ ID NO: 2, and (though optionally) the F box, which corresponds to from about residues 243-285 of SEQ ID NO: 2. In preferred embodiments, the active portion also includes an active site cysteine, such as Cys-813 of SEQ ID NO: 2. The corresponding domains in other cdc4 homologs can be identified by sequence comparison with the human cdc4 protein. Other preferred domains of cdc-4 include domains of the protein which mediate interaction with yet other proteins.

Detailed Description Text - DETX (198):

In one aspect, the present invention provides assays that can be used to screen for drugs which modulate the conjugation of ubiquitin to p27. For instance, the drug screening assays of the present invention can be designed to detect agents which disrupt binding of a SIP protein (such as cdc4), to p27. In other embodiments, the subject assays will identify inhibitors of the enzymatic activity of the SIP ligase, e.g., which inhibitors prevent transfer of ubiquitin from the ligase to p27, or which inhibit the transfer of ubiquitin

from an E2 enzyme, such as UBC2 or UBC3, to a SIP amino acid side chain (e.g., the active site cysteine). In a preferred embodiment, the agent is a mechanism based inhibitor which chemically alters the enzyme, e.g. covalently binds an active site cysteine residue of a SIP ligase, and which is a specific inhibitor of that enzyme, e.g. has an inhibition constant 10-fold, 100-fold, or more preferably, 1000-fold different for other human E3 ligases.

Detailed Description Text - DETX (244):

The present invention also makes available yeast cells which contain a cdc4 null mutation. As described herein, these strains can be complemented using human genes, and thus "humanized" yeast strains can be created for in vivo drug screen, e.g., which comprise a human cdc4 homolog and (optionally) a human p27 or other substrate protein. The strain can be further manipulated to be "humanized" with respect to other biochemical steps in the SIP-mediated ubiquitination of the p27 or G1 phase cyclins (such as a D-type or E-type cyclin). For example, conditional inactivation of the relevant yeast UBC enzyme with concomitant expression of the human UBC homolog, or alternatively, replacement of other yeast genes involved in ubiquitination with their human homologs, provides a humanized system whereby the p27 protein can be ubiquitinated by a mechanism which approximates the cdc4-dependent ubiquitination that occurs in vertebrate cells.

Detailed Description Text - DETX (265):

A GST-fusion protein containing amino acids 696-902 of human cdc4 was used in an in vitro ubiquitination reaction. This reaction also contained E1; one of the following E2's: UBC2, UBC3, UBC4, UBC7 or UBC-myc; and biotinylated ubiquitin for visualization of reaction products with streptavidin conjugated HRP after resolution on non-reducing SDS-PAGE. Under these reaction conditions, cdc4 polypeptide was found to be ubiquitinated by UBC4 and, though to a lesser extent, UBC2. To determine if this ubiquitin conjugation was via a thioester, the reactions were repeated except that prior to separation of the reaction products by SDS-PAGE, one half of the sample was boiled in the presence of a reducing agent. Under these conditions, the ubiquitin was removed from the cdc4 polypeptide, indicating the presence of a labile ubiquitin thiolester bond with the protein. See FIG. 2.

Other Reference Publication - OREF (50):

Zhen et al. (1993) "The ubc-2 Gene of Caenorhabditis elegans Encodes a Ubiquitin-Conjugating Enzyme Involved in Selective Protein Degradation", Mol Cell Biol 13(3):1371-1377.

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FILE 'HOME' ENTERED AT 10:31:08 ON 02 MAY 2005

=> fil .bec
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
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FULL ESTIMATED COST                                         2.10       2.10

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11 FILES IN THE FILE LIST

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           897 UBC##
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                 (UBIQUITIN(W)CONJUGATING(W)ENZYME#)
           103 UBC##
L11         157 UBIQUITIN CONJUGATING ENZYME# OR UBC##

TOTAL FOR ALL FILES
L12       10107 UBIQUITIN CONJUGATING ENZYME# OR UBC##

=> s l12(5a)gene/q
FILE 'MEDLINE'
L13         186 L1 (5A)GENE/Q

FILE 'SCISEARCH'
L14         198 L2 (5A)GENE/Q

FILE 'LIFESCI'
L15         165 L3 (5A)GENE/Q
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```
FILE 'BIOTECHDS'
L16         24 L4  (5A)GENE/Q

FILE 'BIOSIS'
L17        279 L5  (5A)GENE/Q

FILE 'EMBASE'
L18        169 L6  (5A)GENE/Q

FILE 'HCAPLUS'
L19        525 L7  (5A)GENE/Q

FILE 'NTIS'
L20          0 L8  (5A)GENE/Q

FILE 'ESBIOBASE'
L21        147 L9  (5A)GENE/Q

FILE 'BIOTECHNO'
L22        163 L10 (5A)GENE/Q

FILE 'WPIDS'
L23         19 L11 (5A)GENE/Q

TOTAL FOR ALL FILES
L24       1875 L12 (5A) GENE/Q

=> s l12(5a)human
FILE 'MEDLINE'
       1253661 HUMAN
L25        131 L1  (5A)HUMAN

FILE 'SCISEARCH'
       1186243 HUMAN
L26        137 L2  (5A)HUMAN

FILE 'LIFESCI'
        355604 HUMAN
L27         71 L3  (5A)HUMAN

FILE 'BIOTECHDS'
         72038 HUMAN
L28         38 L4  (5A)HUMAN

FILE 'BIOSIS'
       6425996 HUMAN
L29        178 L5  (5A)HUMAN

FILE 'EMBASE'
       5376632 HUMAN
L30        125 L6  (5A)HUMAN

FILE 'HCAPLUS'
       1417589 HUMAN
L31        281 L7  (5A)HUMAN

FILE 'NTIS'
         85247 HUMAN
L32          2 L8  (5A)HUMAN

FILE 'ESBIOBASE'
        436561 HUMAN
L33        109 L9  (5A)HUMAN
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FILE 'BIOTECHNO'
        735552 HUMAN
L34        102 L10(5A)HUMAN

FILE 'WPIDS'
        161270 HUMAN
L35         24 L11(5A)HUMAN

TOTAL FOR ALL FILES
L36       1198 L12(5A) HUMAN

=> s l24 and l36
FILE 'MEDLINE'
L37         37 L13 AND L25

FILE 'SCISEARCH'
L38         37 L14 AND L26

FILE 'LIFESCI'
L39         36 L15 AND L27

FILE 'BIOTECHDS'
L40         16 L16 AND L28

FILE 'BIOSIS'
L41         67 L17 AND L29

FILE 'EMBASE'
L42         34 L18 AND L30

FILE 'HCAPLUS'
L43        178 L19 AND L31

FILE 'NTIS'
L44          0 L20 AND L32

FILE 'ESBIOBASE'
L45         31 L21 AND L33

FILE 'BIOTECHNO'
L46         33 L22 AND L34

FILE 'WPIDS'
L47         10 L23 AND L35

TOTAL FOR ALL FILES
L48        479 L24 AND L36

=> s l48 not 2001-2005/py
FILE 'MEDLINE'
       2400488 2001-2005/PY
L49         31 L37 NOT 2001-2005/PY

FILE 'SCISEARCH'
       4464729 2001-2005/PY
L50         32 L38 NOT 2001-2005/PY

FILE 'LIFESCI'
        422468 2001-2005/PY
L51         28 L39 NOT 2001-2005/PY

FILE 'BIOTECHDS'
         98620 2001-2005/PY
L52         11 L40 NOT 2001-2005/PY
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FILE 'BIOSIS'
       2161950 2001-2005/PY
L53          43 L41 NOT 2001-2005/PY

FILE 'EMBASE'
       2051130 2001-2005/PY
L54          29 L42 NOT 2001-2005/PY

FILE 'HCAPLUS'
       4511505 2001-2005/PY
L55          80 L43 NOT 2001-2005/PY

FILE 'NTIS'
         64180 2001-2005/PY
L56           0 L44 NOT 2001-2005/PY

FILE 'ESBIOBASE'
       1248917 2001-2005/PY
L57          26 L45 NOT 2001-2005/PY

FILE 'BIOTECHNO'
        368875 2001-2005/PY
L58          30 L46 NOT 2001-2005/PY

FILE 'WPIDS'
       4059494 2001-2005/PY
L59           5 L47 NOT 2001-2005/PY

TOTAL FOR ALL FILES
L60         315 L48 NOT 2001-2005/PY

=> fil .becpat
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    17.53      19.63

FILES 'BIOTECHDS, HCAPLUS, WPIDS' ENTERED AT 10:40:22 ON 02 MAY 2005
ALL COPYRIGHTS AND RESTRICTIONS APPLY.  SEE HELP USAGETERMS FOR DETAILS.

3 FILES IN THE FILE LIST

=> s l48 and wo/pc and pry<=2000 and py>2001 range=2004,
FILE 'BIOTECHDS'
          8593 WO/PC
           907 PRY<=2000
                 (PRY<=2000)
         38350 PY>2001
                 (PY>2001)
L61           0 L40 AND WO/PC AND PRY<=2000 AND PY>2001

FILE 'HCAPLUS'
         73562 WO/PC
         68013 PRY<=2000
       1464636 PY>2001
L62          11 L43 AND WO/PC AND PRY<=2000 AND PY>2001

FILE 'WPIDS'
        154034 WO/PC
         57874 PRY<=2000
                 (PRY<=2000)
       1093467 PY>2001
                 (PY>2001)
L63           0 L47 AND WO/PC AND PRY<=2000 AND PY>2001
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TOTAL FOR ALL FILES
L64 11 L48 AND WO/PC AND PRY<=2000 AND PY>2001

=> d tot

L64 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Gene expression profiles and biomarkers for the detection of Alzheimer's disease-related and other disease-related gene transcripts in blood
SO U.S. Pat. Appl. Publ., 155 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO
IN Liew, Choong-chin
AN 2005:325595 HCAPLUS
DN 142:353388

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI US 2005079514	A1	20050414	US 2004-812827	20040330	<--
US 2004014059	A1	20040122	US 2002-268730	20021009	<--
US 2004248169	A1	20041209	US 2004-812737	20040330	<--
US 2004265869	A1	20041230	US 2004-812716	20040330	<--
WO 2004112589	A2	20041229	WO 2004-US20836	20040621	<--

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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

L64 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Sequences of human schizophrenia related genes and use for diagnosis, prognosis and therapy
SO U.S. Pat. Appl. Publ., 156 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO
IN Liew, Choong-chin
AN 2005:248644 HCAPLUS
DN 142:274057

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI US 2004241727	A1	20041202	US 2004-812731	20040330	<--
US 2004014059	A1	20040122	US 2002-268730	20021009	<--
US 2004241727	A1	20041202	US 2004-812731	20040330	<--
US 2004248169	A1	20041209	US 2004-812737	20040330	<--
WO 2004112589	A2	20041229	WO 2004-US20836	20040621	<--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

L64 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Sequences of human schizophrenia related genes and use for diagnosis, prognosis and therapy
SO U.S. Pat. Appl. Publ., 156 pp., Cont.-in-part of U.S. Ser. No. 802,875.

CODEN: USXXCO
IN Liew, Choong-Chin
AN 2005:248643 HCAPLUS
DN 142:274056

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2004241727	A1	20041202	US 2004-812731	20040330 <--
US 2004014059	A1	20040122	US 2002-268730	20021009 <--
US 2004241727	A1	20041202	US 2004-812731	20040330 <--
US 2004248169	A1	20041209	US 2004-812737	20040330 <--
WO 2004112589	A2	20041229	WO 2004-US20836	20040621 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

L64 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Gene expression profiles and biomarkers for the detection of asthma-related and other disease-related gene transcripts in blood
SO U.S. Pat. Appl. Publ., 156 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO
IN Liew, Choong-Chin
AN 2005:160724 HCAPLUS
DN 142:259424

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2005042630	A1	20050224	US 2004-816357	20040401 <--
US 2004014059	A1	20040122	US 2002-268730	20021009 <--
US 2004248169	A1	20041209	US 2004-812737	20040330 <--
US 2004265869	A1	20041230	US 2004-812716	20040330 <--
US 2005042630	A1	20050224	US 2004-816357	20040401 <--
US 2005042630	A1	20050224	US 2004-816357	20040401 <--
WO 2004112589	A2	20041229	WO 2004-US20836	20040621 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

L64 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Gene expression profiles and biomarkers for the detection of hyperlipidemia and other disease-related gene transcripts in blood
SO U.S. Pat. Appl. Publ., 155 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO
IN Liew, Choong-Chin
AN 2005:156681 HCAPLUS
Correction of: 2005:60757
DN 142:216629
Correction of: 142:132329

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI US 2004248170 A1 20041209 US 2004-812777 20040330 <--
US 2004014059 A1 20040122 US 2002-268730 20021009 <--
US 2004248169 A1 20041209 US 2004-812737 20040330 <--
US 2004248170 A1 20041209 US 2004-812777 20040330 <--
US 2004248170 A1 20041209 US 2004-812777 20040330 <--
US 2004265869 A1 20041230 US 2004-812716 20040330 <--
WO 2004112589 A2 20041229 WO 2004-US20836 20040621 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

L64 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Quantitative RT-PCR method for the detection in blood of microarray-identified rheumatoid arthritis-related gene transcripts for diagnosing and monitoring disease state
SO U.S. Pat. Appl. Publ., 81 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO
IN Liew, Choong-Chin
AN 2005:156228 HCAPLUS
Correction of: 2005:16967
DN 142:192331
Correction of: 142:108390

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2005003394	A1	20050106	US 2004-812782	20040330 <--
US 2004014059	A1	20040122	US 2002-268730	20021009 <--
US 2004248169	A1	20041209	US 2004-812737	20040330 <--
US 2004265869	A1	20041230	US 2004-812716	20040330 <--
US 2005003394	A1	20050106	US 2004-812782	20040330 <--
US 2005003394	A1	20050106	US 2004-812782	20040330 <--
WO 2004112589	A2	20041229	WO 2004-US20836	20040621 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

L64 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
TI Gene expression profiles and biomarkers for the detection of Chagas disease and other disease-related gene transcripts in blood
SO U.S. Pat. Appl. Publ., 154 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO
IN Liew, Choong-Chin
AN 2005:60760 HCAPLUS
Correction of: 2004:1036573
DN 142:153477
Correction of: 142:16776

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2004241729	A1	20041202	US 2004-813097	20040330 <--

US 2004014059	A1	20040122	US 2002-268730	20021009 <--
US 2004241729	A1	20041202	US 2004-813097	20040330 <--
US 2004241729	A1	20041202	US 2004-813097	20040330 <--
US 2004248169	A1	20041209	US 2004-812737	20040330 <--
US 2004265869	A1	20041230	US 2004-812716	20040330 <--
WO 2004112589	A2	20041229	WO 2004-US20836	20040621 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

L64 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

TI Gene expression profiles and biomarkers for the detection of lung disease-related and other disease-related gene transcripts in blood

SO U.S. Pat. Appl. Publ., 155 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO

IN Liew, Choong-Chin

AN 2005:60759 HCAPLUS
Correction of: 2004:1036572

DN 142:111840
Correction of: 142:16824

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004241728	A1	20041202	US 2004-812764	20040330 <--
US 2004014059	A1	20040122	US 2002-268730	20021009 <--
US 2004241728	A1	20041202	US 2004-812764	20040330 <--
US 2004241728	A1	20041202	US 2004-812764	20040330 <--
US 2004248169	A1	20041209	US 2004-812737	20040330 <--
US 2004265869	A1	20041230	US 2004-812716	20040330 <--
WO 2004112589	A2	20041229	WO 2004-US20836	20040621 <--

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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

L64 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

TI Analysis of genetic information contained in peripheral blood for diagnosis, prognosis and monitoring treatment of allergy, infection and genetic disease in human

SO U.S. Pat. Appl. Publ., 155 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO

IN Liew, Choong-Chin

AN 2005:60755 HCAPLUS
Correction of: 2004:1036570

DN 142:154259
Correction of: 142:36938

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004241726	A1	20041202	US 2004-812707	20040330 <--
US 2004014059	A1	20040122	US 2002-268730	20021009 <--

US 2004241726	A1	20041202	US 2004-812707	20040330 <--
US 2004241726	A1	20041202	US 2004-812707	20040330 <--
US 2004248169	A1	20041209	US 2004-812737	20040330 <--
US 2004265869	A1	20041230	US 2004-812716	20040330 <--
WO 2004112589	A2	20041229	WO 2004-US20836	20040621 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

L64 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

TI Sequences of human schizophrenia related genes and use for diagnosis, prognosis and therapy

SO U.S. Pat. Appl. Publ., 156 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO

IN Liew, Choong-Chin

AN 2005:60754 HCAPLUS
Correction of: 2004:1036571

DN 142:233342
Correction of: 142:16836

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004241727	A1	20041202	US 2004-812731	20040330 <--
US 2004014059	A1	20040122	US 2002-268730	20021009 <--
US 2004241727	A1	20041202	US 2004-812731	20040330 <--
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TI Gene expression profiles and biomarkers for the detection of depression-related and other disease-related gene transcripts in blood

SO U.S. Pat. Appl. Publ., 154 pp., Cont.-in-part of U.S. Ser. No. 802,875.
CODEN: USXXCO

IN Liew, Choong-Chin

AN 2005:1997 HCAPLUS

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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004265868	A1	20041230	US 2004-812702	20040330 <--
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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	24.07	43.70

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